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American Heart Journal

VOL. 43 JANUARY, 1952 NO. 1

Editorial

FOR over twenty-six years, this JOURNAL has held its place among the scientific publications of North America. On its pages there have appeared accounts of many significant advances in our understanding of the circulation. Such contributions would, in the nature of things, stimulate increasing study and investigations over an ever-widening frontier. This has been evident in many other countries, and since medical as well as other scientific pursuits know no geographical boundaries, a community of interests has steadily grown.

This community of interests was first shown in the creation of National Societies or Associations whose aim was the exchange of knowledge concerning cardiology in particular and the circulation of the blood in general. The next forward step was a regional federation of societies, such as the Inter-American Society of Cardiology, which will hold its fourth meeting in Buenos Aires, from Sept. 1 to 6, 1952, under the auspices of the Cardiological Society of Argentina. The distinguished physician, Dr. Pedro Cossio, will be President of the Congress.

The world-wide upsurge of interest in diseases of the circulation found a natural expression in the initiation of an International Congress of Cardiology, which held its first meeting in Paris in September, 1950.

The Editorial Board of the AMERICAN HEART JOURNAL, fully appreciative of the widening interest of its readers in the investigations of their colleagues, published a review of the Scientific Proceedings of the Congress, under the able guidance of Demetrio Sodi-Pallares and Jorge Espino-Vela, in the April and May numbers of Volume 41, 1951. The Board, during the past summer, gave much thought to its own expansion and finally decided to invite outstanding cardiologists in Europe and the Americas to participate in the creation of an International Editorial Board. The unanimous response to the invitation was most gratifying and justified the belief of the Board in the community of scientific interest in the study of the circulation. To all of our new associates we wish to extend a sincere welcome and our thanks for their ready acceptance of this additional task.

Consideration was also given to the advisability of changing the name of the JOURNAL to denote the expanding scope of its interests. This was decided against. The AMERICAN HEART JOURNAL has become a familiar name and has meant much during its long career. It will still be a symbol to its readers, although the Editorial family has grown larger and its geographical area has extended.

Original Communications

CLINICAL AND PHYSIOLOGICAL CORRELATIONS IN PATIENTS WITH MITRAL STENOSIS. V.

BENJAMIN M. LEWIS, M.D.,* RICHARD GORLIN, M.D.,** HECTOR E. J. HOUSSAY, M.D.,*** FLORENCE W. HAYNES, PH.D., AND LEWIS DEXTER, M.D.

BOSTON, MASS.

THERE are three pathological sources of disability in mitral stenosis: the narrowed valve orifice, the histological changes in the pulmonary arterioles,[1] and the diseased myocardium resulting from active or smoldering rheumatic carditis. The development of cardiac catheterization,[2] the ability to measure pulmonary "capillary" pressure,[3] which has been found equivalent to left auricular pressure,[4] and the application of hydraulic formulas to living systems[5] have made it possible to quantitate two of these factors, the size of the mitral valve orifice and the amount of narrowing of the pulmonary vascular bed, reflected physiologically in the calculated pulmonary arteriolar resistance.

In previous publications Gorlin and associates[5,6] presented evidence that the mitral valve area calculated from physiological data agrees closely with the area measured directly and analyzed the physiological consequences of mitral stenosis from a hydraulic point of view, emphasizing the interrelation of pressure behind the valve and peripheral blood flow. Earlier, Dexter and co-workers[7] had drawn attention to the significant role which narrowing of the small pulmonary arteries (that is, increase in pulmonary arteriolar resistance) plays in the body's adaptation to this disease. The present report will deal with the relation of clinical findings to the two factors—narrowing of the mitral valve and changes in the pulmonary arterioles—and attempt to connect the various manifestations of the patient's disease with the physiological changes which these two factors impose on the patient.

Such an attempt to correlate clinical findings with the degree of anatomical stenosis and with the severity of accompanying pulmonary vascular disease assumes considerable importance at this time because of the recent interest in

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*Research Fellow of the American Heart Association. This work was done in part during the tenure of a Fellowship from the Dazian Foundation for Medical Research.

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***Research Fellow of the Rockefeller Foundation.

operative attacks upon the diseased mitral valve. That such operations are now practical is attested to by reports from several surgical centers.[8-10] It is therefore desirable to predict from the results of comprehensive clinical examination the approximate degree of stenosis present and thus to evaluate the severity of the mechanical obstacle which surgical interference seeks to overcome.

MATERIALS AND METHODS

In order that such a study may give meaningful results, it is necessary, first of all, to analyze only frequently recurrent or constantly present elements in the clinical picture, for only these can be related to a given narrowing of the mitral valve and a given degree of pulmonary vascular obstruction. As Gorlin and co-workers[11] have clearly pointed out, conditions demanding increased cardiac output, such as thyrotoxicosis or anemia and tachycardias arising from any cause, will exaggerate the physiological alterations brought about by mitral stenosis and hence will aggravate the symptoms present. Such events may be responsible for sudden peaks in the symptomatology of mitral stenosis, and, consequently, the patient's condition at such a time will not reflect the anatomical change present in the mitral valve and in the pulmonary arterioles. For this reason the present report will analyze the "constantly present" or "frequently recurrent" features in the clinical state of thirty patients with pure mitral stenosis in whom there was no associated condition leading to an increase in cardiac output, in whom the pulse rate was within the physiological range, with no evidence of active rheumatic fever, and who were considered to be under good medical care.

There were twenty-one women and nine men (Table I). Ages ranged from 22 to 61 years, with a mean of 36.2 years. The average duration of heart disease was 16.7 years, the range being from 2 to 38 years. The onset of heart disease was dated from the first attack of rheumatic fever in fourteen patients, from the discovery of a heart murmur in five patients, and from the onset of symptoms in eleven patients. Of the fourteen who had a previous history of rheumatic fever, six were known to have developed congestive heart failure during an attack of rheumatic fever, and nine patients had had multiple attacks of rheumatic fever. All had apical diastolic murmurs, regarded as diagnostic of mitral stenosis. Twelve had apical systolic murmurs, Grade 2+ or more. None of these was considered to have mitral regurgitation, however, this finding being based on physiological criteria involving the height of the V wave in the pulmonary "capillary" pulse tracing,[6] and in five of these twelve patients the absence of regurgitation was confirmed by palpation of the valve at operation.* Eight patients had diastolic murmurs of Grade 2+ or louder along the left sternal border, but in none of these cases was the arterial diastolic blood pressure, measured directly, below 62 mm. Hg. Hence, these patients were considered to have mitral stenosis as the only significant valve lesion. None of the patients had subacute bacterial endocarditis.

All patients had a complete history, physical examination, electrocardiogram with standard and unipolar limb and chest leads, seven-foot heart film, and cardiac fluoroscopy prior to cardiac catheterization which was performed by the

*By Dr. Dwight E. Harken.

TABLE I. CLINICOPHYSIOLOGICAL DATA

VITAL DATA			PHYSIOLOGICAL MEASUREMENTS						HISTORY			
				RESISTANCE (DYNES SECONDS CM.$^{-5}$)			MEAN PRESSURES (MM. Hg)					
NAME	AGE	SEX	MITRAL VALVE AREA (CM.^{2})	PULMONARY ARTERIOLAR	TOTAL PULMONARY	CARDIAC INDEX (LITERS PER MINUTE PER SQ. M.)	PULMONARY ARTERY	RIGHT ATRIUM	SEVERITY OF DYSPNEA	FATIGUE	PAROXYSMAL NOCTURNAL DYSPNEA	HEMOPSTYSE
J. D.*	30	M	2.5	51	212	5.2	25	9	1+	0	0	0
F. C.	23	M	2.5	68	195	4.3	20	3	1+	0	0	0
J. F.*	61	M	1.6	135	394	3.8	32	9	1+	+	0	0
L. B.*	32	F	1.4	67	400	3.3	24	4	1+	0	0	0
L. C.*	32	F	1.4	711	1110	3.3	75	9	4+	0	+	+
J. M.*	22	M	1.3	145	600	2.7	33	0	1+	0	0	0
Gr.*	37	F	1.1	114	480	4.6	42	8	3+	0	+	+
N. W.	40	F	1.0	204	684	3.2	47	2	3+	+	0	0
R. C.*	33	F	0.9	544	1130	3.5	75	5	4+	0	+	0
L. T.*	43	M	0.9	382	820	2.5	45	5	3+	0	+	+
Ba.*	33	F	0.9	569	1062	3.6	69	−3	3+	0	+	+
M. B.*	47	F	0.8	150	574	2.0	23	14	4+		+	0
S. V.	40	F	0.7	428	1078	3 0	58	8	3+	0	0	+
T. C.	25	F	0.7	488	1171	2.9	60	10	2+	0	0	0
L. L.	28	F	0.7	632	1202	2.5	57	5	2+	0	0	0
M. T.*	32	F	0.7	225	750	2.4	30	5	4+	0	+	+
E. S.*	43	F	0.7	451	984	2.4	48	4	3+	0	+	0
J. G.	28	M	0.6	391	1054	2.1	54	10	4+	0	+	0
W. F.*	39	F	0.6	1139	1845	1.8	60	8	4+	0	+	0
E. D.*	42	F	0.6	411	1235	2.4	54	12	3+	0	0	0
McL.*	41	M	0.6	762	1790	2.4	94	33	2+	0	0	0
R. W.*	37	F	0.6	274	1050	2.6	46	9	4+	0	0	0
N. L.*	33	M	0.6	950	1650	1.9	66	14	4+	0	+	0
M. G.*	42	F	0.6	1480	2372	2.0	80	15	4+		+	0
D. K.*	33	F	0.5	256	1730	1.8	54	4	4+	0	+	0
McN.	36	M	0.5	853	1736	1.8	65	13	2+	+	0	0
M. M.*	40	F	0.4	1150	1915	1.4	55	10	4+	0	+	0
H. W.	47	F	0.4	1662	2640	1.6	86	21	4+	0	+	0
McG.	43	F	0.4	769	1537	1.8	50	4	4+	+	+	0
D. V.*	23	F	0.4	746	1680	2.6	63	7	2+	+	0	0

*Previously reported.[6]
†Cuff method.
‡NSR = normal sinus rhythm.
AF = auricular fibrillation.

IN PATIENTS WITH MITRAL STENOSIS

PHYSICAL EXAMINATION					ROENTGENOGRAPHIC EXAMINATION				ELECTROCARDIOGRAM			
GRADE OF MURMUR			EDEMA	HEPATOMEGALY	HEART SIZE (% ENLARGEMENT)	LEFT AURICLE		PULMONARY ARTERY DILATATION	RHYTHM	ABNORMAL P WAVES	RIGHT VENTRICULAR HYPERTROPHY	RIGHT BUNDLE BRANCH BLOCK
APICAL DIASTOLIC	APICAL SYSTOLIC	BASAL DIASTOLIC				DILATATION	PULSATION					
1+	0	0	0	0	+6	Slight	0	1+	NSR‡	0	0	0
1+	3+	0	0	0	0	Moderate	+	0	NSR	0	0	0
2+	2+	0	0	0	+12	Moderate	0	0	NSR	+	0	0
4+	0	0	0	0	0	Moderate	+	0	NSR	0	0	0
4+	0	0	0	0	0	Slight	0	4+	NSR	+	+	0
5+	2+	0	0	0	+32	Marked	0	2+	NSR	+	+	0
2+	1+	1+ (112/62)	0	0	0	Moderate	0	1+	NSR	0	0	0
3+	0	0	+	0	+9	Moderate	0	3+	NSR	+	0	0
3+	0	0	0	0	+10	Moderate	0	2+	NSR	+	+	0
3+	0	0	0	0	+15	Marked	+	3+	NSR	+	0	+
5+	0	0	0	+	<20	Marked	0	1+	NSR	+	+	0
1+	0	0	+	+	+17	Marked	0	1+	AF	—	0	0
1+	0	0	0	0	+25	Moderate	0	0	NSR	0	0	+
2+	3+	2+ (104/77)	0	0	+49	Moderate	+	3+	NSR	0	+	0
3+	2+	3+ (119/69)	0	0	+22	Moderate	0	3+	NSR	+	+	0
2+	3+	2+ (110/70)†	0	+	+6	Marked	0	2+	NSR	0	0	0
3+	0	2+ (110/70)	+	0	+19	Moderate	0	1+	AF	—	0	+
2+	0	0	0	+	+25	Slight	0	2+	AF	—	+	0
2+	0	0	+	+	+50	Moderate	0	2+	AF	—	+	0
1+	2+	0	0	+	+40	Marked	0	3+	AF	—	+	0
2+	4+	4+ (147/104)	0	0	+53	Marked	0	3+	AF	—	+	+
4+	0	0	+	0	+50	Marked	0	2+	NSR	+	+	+
3+	0	0	+	+	+45	Moderate	0	3+	NSR	+	+	0
3+	3+	2+ (135/95)†	+	+	>30	Marked		3+	NSR	0	+	0
2+	0	0	+	0	+20	Marked	0	3+	NSR	0	0	0
5+	2+	1+ (110/76)	+	0	+60	Marked	±	3+	NSR	+	+	0
1+	1+	2+ (118/74)	+	+	+48	Marked	+	2+	AF	—	+	0
1+	3+	0	+	+	>30	Moderate	±	3+	AF	—	+	0
3+	0	2+ (126/81)	0	+	+50	Moderate	+	2+	AF	—	+	0
4+	2+	0	0	+	+50	Moderate	0	4+	NSR	0	+	+

TABLE II. PHYSIOLOGICAL DATA IN PATIENTS WITH MITRAL STENOSIS*

PATIENT	BODY SURFACE AREA (SQ. M.)	OXYGEN CONSUMPTION (C.C. PER MINUTE)	A-V OXYGEN DIFFERENCE (C.C. PER LITER)	CARDIAC INDEX (LITERS PER MINUTE PER SQ. M.)	STROKE INDEX (C.C PER MINUTE PER SQ. M.)	A-P DIAMETER OF CHEST (CM.)	MEAN PRESSURES (MM. Hg)				RESISTANCES (DYNES SECONDS CM.$^{-5}$)			DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	MITRAL VALVE FLOW (C.C. PER DIASTOLIC SECOND)	MITRAL VALVE AREA (CM.^{2})
							PULMONARY ARTERY	PULMONARY "CAPILLARY"	BRACHIAL ARTERY	RIGHT AURICLE	PULMONARY ARTERIOLAR	TOTAL PULMONARY	TOTAL SYSTEMIC			
F. C.	1.92	286	35	4.3	51	19	20	13	90	3	68	195	878	37.7	217	2.5
N. W.	1.71	227	41	3.2	39	20	47	33	97	2	204	684	1412	35.0	157	1.0
S. V.	1.45	202	47	3.0	28	19	58	35	93	8	428	1078	1732	34.2	126	0.7
T. C.	1.39	245	60	2.9	29	15	60	35	92	10	488	1171	1792	36.0	114	0.7
L. L.	1.50	198	52	2.5	35	19	57	27	87	5	632	1202	1834	38.8	98	0.7
J. G.	1.92	293	72	2.1	20		54	34	84	10	391	1054	1637	39.2	104	0.6
McN.	1.67	283	93	1.8	24	18	65	33	86	13	853	1736	2292	37.4	80	0.5
McG.	1.48	193	75	1.8	20	18	50	25	95	4	769	1537	2920	39.6	66	0.4
H. W.	1.65	201	78	1.6	18	20	86	32	126	21	1662	2640	3890	36.0	72	0.4

*Patients for whom these data have not been previously published.[6]

usual technique and included the determination of pulmonary "capillary" pressure.[3] Pressures were measured by Hamilton manometers[12] or by electromanometers.*[13] Cardiac outputs were determined by the direct Fick method.

Mitral valve area was calculated by the formula:

$$MVA = \frac{MVF}{31\sqrt{\text{"PC"} - 5}}$$

where MVA = area of the mitral valve in cm.^{2}
MVF = mitral valve flow in c.c. per diastolic second
"PC" = pulmonary "capillary" mean pressure in mm. Hg
5 = assumed left ventricular diastolic pressure in mm. Hg
31 = empirical constant.

Pulmonary arteriolar resistance was calculated by the formula:

$$R = \frac{PA_m - \text{"}PC_m\text{"}}{CO} \times 1{,}332$$

and total pulmonary resistance was calculated by the formula:

$$R = \frac{PA_m}{CO} \times 1{,}332$$

where R = resistance in dynes seconds cm.$^{-5}$
PA_m = pulmonary arterial mean pressure in mm. Hg
"PC_m" = pulmonary "capillary" mean pressure in mm. Hg
1,332 = constant for conversion to absolute units
CO = cardiac output in c.c. per second.

Details of these calculations are given elsewhere.[5,7]

The physiological data from which these calculations were made have been published by Gorlin and associates[6] for twenty-one of these patients. The data for the nine other patients are given in Table II.

RESULTS

Physiological Interrelations.—The relation between a narrow mitral valve and symptoms in a patient with mitral stenosis lies in the physiological changes which the narrowed valve imposes on the patient. The first such change is a rise in pressure behind the narrowed orifice, i.e., in the left auricle and pulmonary capillaries. It is this pressure which is responsible for most of the pulmonary symptoms in patients with mitral stenosis. In Fig. 1 (left), the relation of orifice size to pulmonary "capillary" (or left atrial) pressure and to blood flow is shown. At a normal mitral valve area of 4.0 cm.^{2} a normal valve flow of 150 c.c. per diastolic second can be accomplished at a low pressure head. Great increases in flow are possible with small increases in left atrial pressure. A patient with mild

*Sanborn Company, Cambridge, Mass.

mitral stenosis, e.g., with a valve area of 2.5 cm.², can accomplish a normal resting flow at a low pulmonary "capillary" pressure, but an appreciable increase in flow, the result, for example, of severe exercise, can bring him to the "pulmonary edema" threshold at which the capillary pressure becomes equal to the plasma osmotic pressure. When the stenosis has advanced to a valve area of 1.0 cm.², an elevated pressure in the left atrium and pulmonary vasculature is required even at rest, and despite great increases in pressure, little increase in flow is possible.

PHYSIOLOGIC RELATIONS IN MITRAL STENOSIS

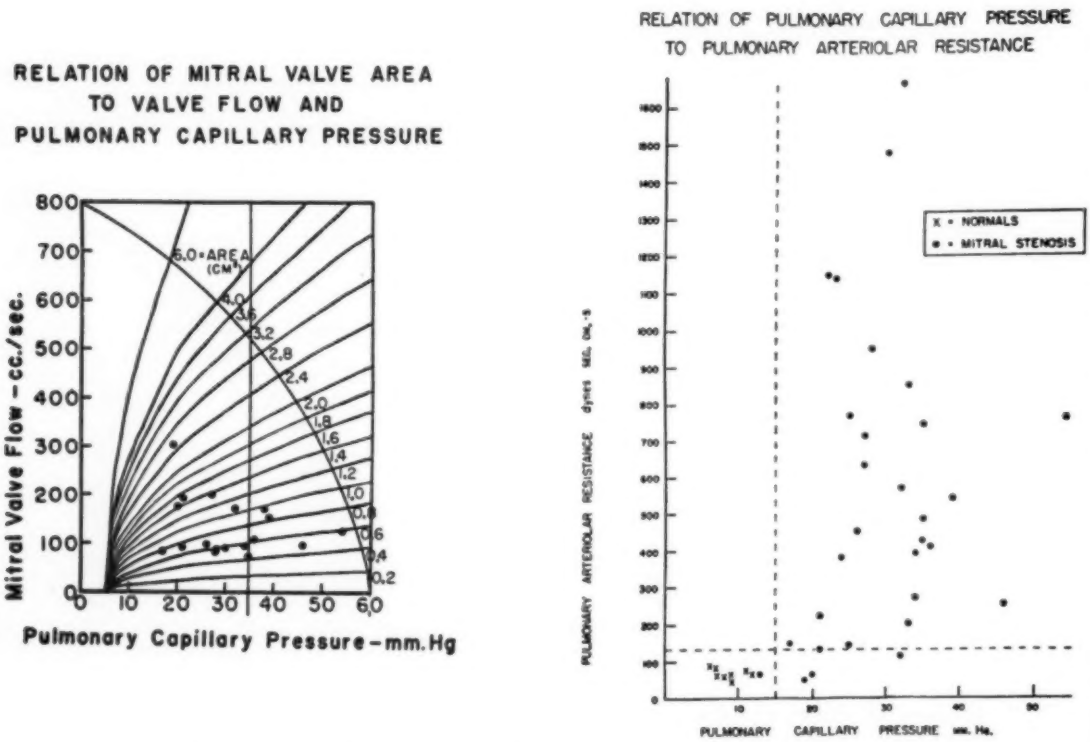

Fig. 1.—The figure on the left is taken from the paper by Gorlin and Gorlin.[5] Note the increase in pressure necessary to secure a given flow as the valve becomes smaller and, especially, the great increases in pressure needed for small increases in flow at valve areas below 1.0 cm.² The figure on the right is modified from Dexter and associates.[7] The abrupt increase of pulmonary arteriolar resistance at pulmonary "capillary" pressures above 25 mm. Hg should be noted.

Thus, the transition from a normal mitral valve to a severely narrowed one is marked by the increase in pressure behind the valve required to secure a given flow. When the valve area is 1.0 cm.², the pulmonary capillary pressure needed for a normal resting flow virtually equals the plasma osmotic pressure (25 mm. Hg). The maintenance of a pressure appreciably above this level for any length of time will be followed by the occurrence of pulmonary edema.[11] To avoid this, a fall in blood flow occurs as a second physiological compensation. The linear

decrease of cardiac index with a narrowing valve is shown in Fig. 2 (upper left), in which the regression line intersects the lower limit of cardiac index for this laboratory (2.8 L. per minute per square meter) at a valve area of 1.0 cm.^{2}

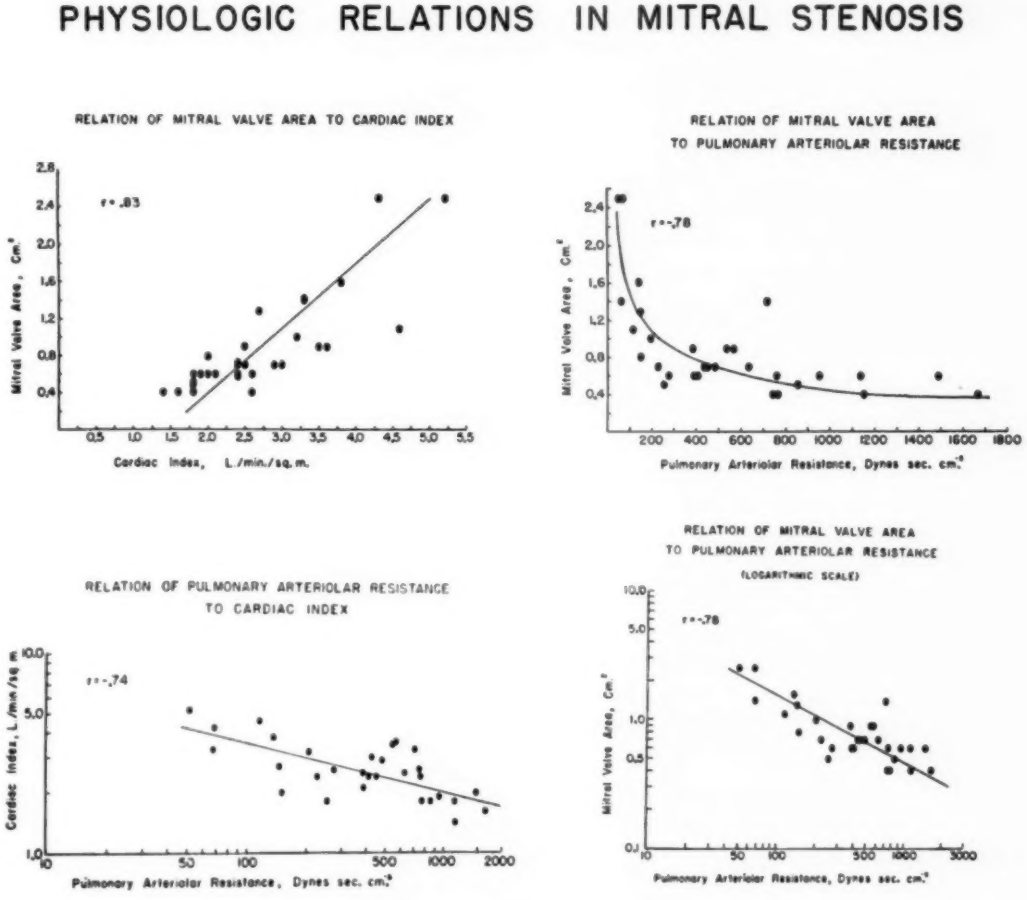

Fig. 2.—The two figures on the left illustrate the decrease in cardiac output produced by the narrowing of the mitral valve and the increase of pulmonary arteriolar resistance. The relation between pulmonary arteriolar resistance and cardiac index is logarithmic. On the right, the relation of mitral valve area to pulmonary arteriolar resistance is shown. The hyperbolic curve above is plotted with values derived from the equation of the line in the lower figure, which shows the logarithmic relation between these two factors.

At this point, when the stenosis is already far advanced, a third physiological mechanism is added to the reciprocal changes in pressure and flow that take place at a valve area of about 1.0 cm.^{2} This is a narrowing of the pulmonary arterioles, first described by Parker and Weiss,[1] which is measured in these studies as an increase in pulmonary arteriolar resistance. The relation of this measurement to pulmonary "capillary" pressure is shown in Fig. 1 (right). As the pulmonary "capillary" pressure reaches 25 mm. Hg (that is, approaches the osmotic pressure of plasma), there is a variable increase in pulmonary arteriolar resistance. This increase in pulmonary arteriolar resistance tends to decrease the output of the

right ventricle as shown in Fig. 2 (lower left), in which the inverse logarithmic relation of cardiac index to pulmonary arteriolar resistance is demonstrated. The decrease in cardiac index, in turn, leads to a decrease in the pressure head required in the left atrium and in the pulmonary capillaries. Hence, as Dexter and associates have previously stated,[7] "Increased pulmonary arteriolar resistance is a compensatory mechanism preventing to some extent increase in flow through the capillaries to the narrow mitral valve and therefore protecting the pulmonary capillaries from a high hydrostatic pressure and pulmonary edema."

The course of mitral stenosis, considered as a mechanical disease, is thus concerned with two areas of resistance. The first is the mitral valve itself, which as it narrows requires a high pressure in the left atrium and lungs, thereby producing many of the disabling pulmonary symptoms; the second is a narrowing of the small arterioles of the lungs which appears late in the course of the disease. As will be apparent later, it is not until this resistance is added to that of the mitral valve that the right ventricle fails. It is mainly these two factors which influence the symptomatology of mitral stenosis.

The interrelation of these factors—mitral valve area and pulmonary arteriolar resistance—is shown in Fig. 2 (upper right) and is a roughly hyperbolic curve since a significant straight-line logarithmic relation exists between these variables (Fig. 2, lower right). Such a relation follows from the principles already discussed, namely that a mitral valve of 1.0 cm.^{2} or less requires an elevation of pulmonary "capillary" pressure even at rest, and that an elevation of pulmonary "capillary" pressure in turn leads to an increase in pulmonary arteriolar resistance.

In the clinicophysiological studies of mitral stenosis, we shall be interested chiefly in two areas on this curve. The first lies at a valve area of about 1.0 cm.^{2} at which a narrowed valve and slight to moderate increases in pulmonary arteriolar resistance exist in the same patient. The second is that portion of the curve which becomes asymptotic to the pulmonary arteriolar resistance, where a very narrow valve and extreme elevations of pulmonary arteriolar resistance are found together.

In considering the symptomatic picture of mitral stenosis then, three related physiological mechanisms must be kept in mind. As the mitral valve narrows, more pressure is required for a given flow. To maintain a normal resting flow at a valve area of 1.0 cm.^{2} requires a pressure close to the osmotic pressure of plasma. Cardiac output decreases in a linear fashion as the mitral valve grows smaller. At this point, when the stenosis is far advanced, an increase in pulmonary arteriolar resistance occurs, presumably as a compensatory mechanism protecting the pulmonary capillaries against hydrostatic pressure. But this mechanism is a two-edged sword. While protecting the capillaries from sudden increases in pressure, it further decreases cardiac output and increases the work load of the right ventricle.

Exertional Dyspnea.—The symptom of dyspnea is admittedly difficult to evaluate because it is essentially subjective and because of the lack of agreement on the physiological alterations underlying it. Most reviewers of the subject, however (e.g., Altschule[14]), believe that it stems both from pulmonary congestion and from decreased peripheral cardiac output.

In Fig. 3 (upper left) those patients with little dyspnea who could carry on relatively normal lives (1+ dyspnea) are shown clustered about the vertical asymptote of the curve relating mitral valve area to pulmonary arteriolar resistance. Thus they had neither severe stenosis, the values ranging from 1.3 to 2.5 cm.^{2}, nor significant increases of pulmonary arteriolar resistance, all values being below 145 dynes seconds cm.$^{-5}$

RELATION OF MITRAL VALVE AREA AND PULMONARY ARTERIOLAR RESISTANCE TO PULMONARY SYMPTOMS IN MITRAL STENOSIS

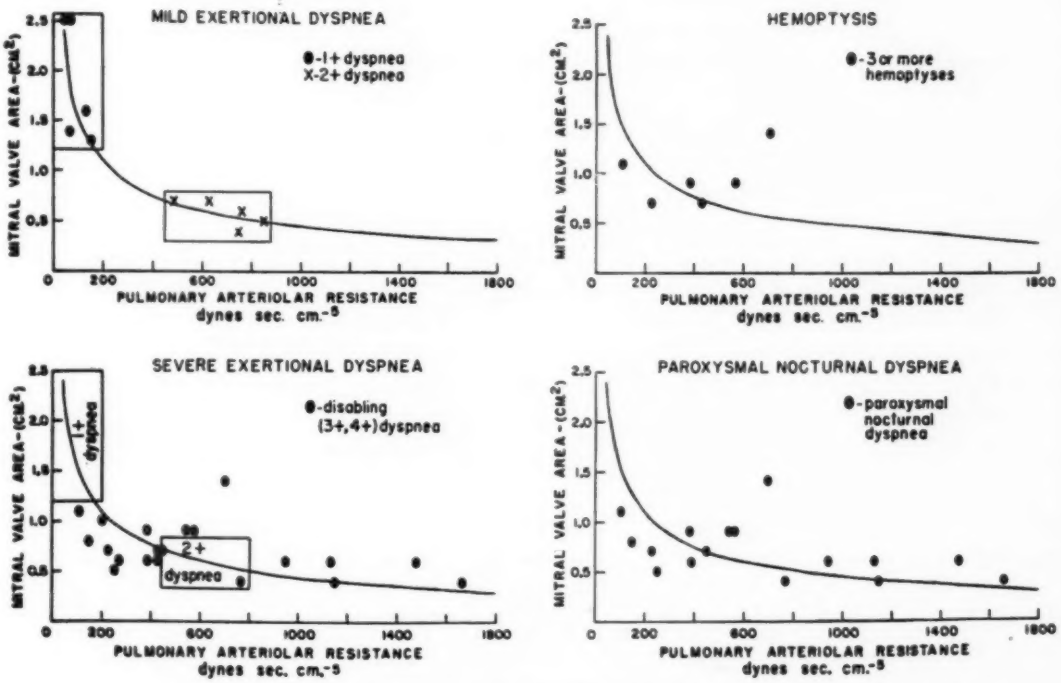

Fig. 3.—Patients with various pulmonary symptoms are plotted in relation to the curve which relates mitral valve area and pulmonary arteriolar resistance (Fig. 2). Note that severe symptoms are found in patients with valve areas of 1.0 cm.^{2} and smaller. See text for the relation of pulmonary arteriolar resistance to symptom production.

With increasing severity of stenosis, although the concomitant increase in pulmonary arteriolar resistance was still relatively slight, there was a rather sharp increase in symptomatology. All thirteen patients who grouped about the bend of the curve, in whom a severe stenosis (0.5 to 1.1 cm.^{2}) was combined with slight elevations of pulmonary arteriolar resistance (150 to 569 dynes seconds cm.$^{-5}$), were disabled by dyspnea, being unable to work or perform even light household tasks (3+ and 4+ dyspnea) (Fig. 3, lower left).

In contrast to this group, the five patients who had moderate elevations of pulmonary arteriolar resistance (488 to 853 dynes seconds cm.$^{-5}$) combined with

severe stenosis (0.5 to 0.7 cm.^{2}), while dyspneic on ordinary efforts, were still able to work at light occupations (2+ dyspnea) (Fig. 2, upper left). A still further increase in pulmonary arteriolar resistance (from 711 to 1,662 dynes seconds cm.$^{-5}$), however, was accompanied by disabling (3+ and 4+) dyspnea in the seven patients who fell into this group (Fig. 3, lower left).

On the basis of our present physiological understanding of mitral stenosis, the disabling exertional dyspnea in those with severe stenosis but slight increase in pulmonary arteriolar resistance may have been related to the ability of the right ventricle, unhampered by a high pulmonary arteriolar resistance, to produce acute congestion of the lungs on attempted exertion. Such an explanation is strengthened by the fact that gross cardiac enlargement was found in only one of these patients, and only one had edema and hepatomegaly as evidence of right ventricular failure.

The occurrence in five patients with severe stenosis and moderate elevations of pulmonary arteriolar resistance of definite, but not disabling, dyspnea is noteworthy. This group may have achieved a precarious balance with the development of pulmonary arteriolar resistance sufficient to protect the lungs from congestion, but insufficient to cause failure of the right ventricle. Cardiac enlargement, however, uniformly characterized this group, and in four of the five patients it was massive.

The disabling dyspnea in the seven patients with great elevations of pulmonary arteriolar resistance and severe stenosis may be related to the reduced cardiac output which such a high resistance imposes or to the high pulmonary arterial pressure which accompanies it and thus resemble the dyspnea seen in pulmonary vascular disease in which congestion of the pulmonary capillary bed is clearly not a factor.[15] With one exception, a patient with a valve area of 1.4 cm.^{2}, all these patients had massively enlarged hearts and palpable livers, and five had edema as well.

Fatigue.—As distinct from dyspnea, easy fatigability, weakness, and exhaustion were prominent complaints in only five patients (Table I). This is in contrast to patients with combined stenosis and insufficiency, in whom these symptoms were predominant in all of those studied.[16] Those patients with pure stenosis who had this complaint were physiologically a mixed group, although three (McM., D. V., McG.) presented the picture of a very narrow valve (0.4 to 0.5 cm.^{2}) and a moderate elevation of pulmonary arteriolar resistance (746 to 853 dynes seconds cm.$^{-5}$).

Hemoptyses.—In six patients, hemoptysis was a prominent symptom. Excluding hemoptyses definitely or probably due to pulmonary infarction, upper respiratory infection, or acute pulmonary edema, each of these patients had had three or more such attacks with expectoration of a cupful or more of blood within the past two years. The relation of this symptom to mitral valve area and to pulmonary arteriolar resistance is shown in Fig. 3 (upper right). Five patients had valve areas close to 1.0 cm.^{2}, ranging from 0.7 to 1.1 cm.^{2}, while in one patient the valve area was 1.4 cm.^{2} Such stenosis necessitates a high pressure in the pulmonary capillaries. At the same time, these five patients had only slight increases of arteriolar resistance, less than 569 dynes seconds cm.$^{-5}$

Physiologically, these patients have a stenosis of such severity that a high pulmonary capillary pressure is necessary even at rest, and little increase in flow is possible despite great increases in pressure. A slight increase in right ventricular output in such patients would result in a great increase in intravascular pressure.[17] These patients with only a slight increase in pulmonary arteriolar resistance have no effective way of preventing such acute increases in right ventricular output and hence of preventing episodes of sudden extreme pulmonary congestion.

The associated clinical findings tend to support the concept that the ability of a relatively strong right ventricle to congest the lungs acutely is responsible for this symptom. Significant cardiac enlargement (20 per cent or more by the standards of Ungerleider and Clark[18]) was found in only one patient, in two the liver was palpable two or more fingerbreadths below the right costal margin, and none was edematous. In contrast, other respiratory symptoms in this group were severe; all were disabled by exertional dyspnea, and five had paroxysmal nocturnal dyspnea.

This hemodynamic interpretation, however, does not explain why other patients with similar physiological adjustments did not have frequent hemoptyses. The work of Ferguson, Kobilak, and Deitrick,[19] who found dilated bronchial veins communicating freely with pulmonary veins in those patients with mitral stenosis who had episodes of hemoptyses, provides a possible reason for this difference, for such varices might represent a *locus minoris resistentiae* which gives way in the face of acute rises in pulmonary venous pressure before pulmonary edema can occur.

Paroxysmal Nocturnal Dyspnea.—The relation of paroxysmal nocturnal dyspnea to the mitral valve area and the pulmonary arteriolar resistance is shown in Fig. 2 (lower right). Each of these sixteen patients had attacks, regarded clinically as typical of paroxysmal nocturnal dyspnea, which occurred twice weekly or at more frequent intervals. Fourteen of these sixteen patients had valve areas of 1.0 cm.^{2} or smaller, emphasizing the importance of this degree of stenosis in the production of symptoms.

The magnitude of the pulmonary arteriolar resistance makes it possible to divide these patients into two rather distinct groups. The first (nine patients) was characterized by having narrow mitral valves (0.5 to 1.1 cm.^{2}), slight increases in pulmonary arteriolar resistance (150 to 569 dynes seconds cm.$^{-5}$) with hearts either normal in size or moderately enlarged, hemoptyses in four patients, and little evidence of right ventricular failure.

The remaining seven patients, while likewise having severe mitral stenosis (under 1.0 cm.^{2} in all but one case in which it was 1.4 cm.^{2}), had great elevations, in pulmonary arteriolar resistance, ranging from 711 to 1,660 dynes seconds cm.$^{-5}$ Cardiac enlargement was massive in six of these, and five were in frank right ventricular failure, both features in marked contrast to the first group.

The syndrome of paroxysmal nocturnal dyspnea probably has a mixed physiological basis corresponding to the variable patterns of arteriolar resistance and valvular stenosis seen in these patients. Reviewers of the subject (e.g., Altschule[14]) believe that most attacks are the result of frank or incipient pul-

monary edema, while others may result from changes of position alone in severely dyspneic or orthopneic patients. The pathogenesis of acute pulmonary edema in mitral stenosis has been analyzed from a hydraulic point of view by Gorlin and associates.[11] Pulmonary edema, in their experience, was always associated with an elevation of the pulmonary "capillary" pressure above the plasma osmotic pressure. The two main factors contributing to this rise were an increase in cardiac output, which demands a higher pressure head in the left auricle and

RELATION OF MITRAL VALVE AREA AND PULMONARY ARTERIOLAR RESISTANCE TO PHYSICAL FINDINGS IN MITRAL STENOSIS

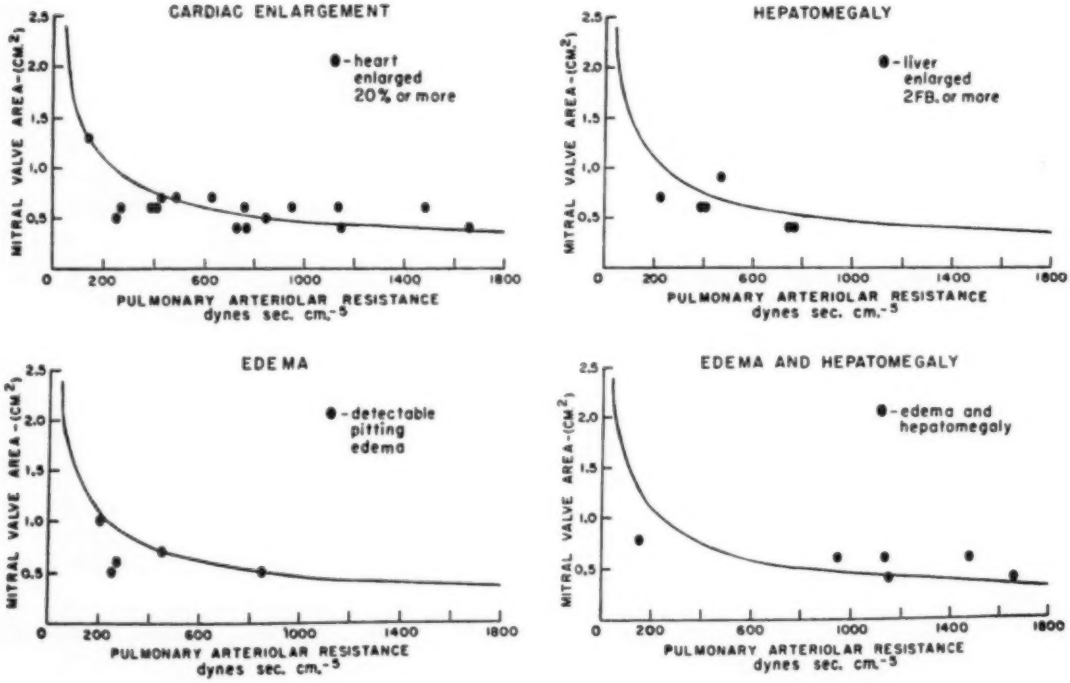

Fig. 4.—Patients with cardiac enlargement and signs of right ventricular failure are plotted against the curve relating mitral valve area to pulmonary arteriolar resistance. The presence of significant cardiac enlargement was confirmed by chest film in all cases. Note that patients with cardiac enlargement and edema and hepatomegaly cluster about the horizontal asymptote of the curve.

lungs, and tachycardia, which, by shortening the time for filling of the left ventricle, also demands a greater flow per unit of time through the mitral valve and thus a higher pressure in the left auricle and pulmonary capillaries. Those patients in the first group, with a relatively low pulmonary arteriolar resistance and little cardiac enlargement, can acutely increase cardiac output in the face of such stimuli as the increased blood volumes that accompany sleep (Perera and Berliner[20]), and the occurrence of paroxysmal nocturnal dyspnea in these patients

can be attributed to acute increases in pulmonary congestion, not infrequently to the point of pulmonary edema. The patients in the second group, in whom the influence of a high pulmonary arteriolar resistance and a dilated heart act to depress cardiac output, may experience this symptom from a change in position, since all are severely orthopneic, or from a tachycardia, which, as Gorlin and coworkers[11] have emphasized, can lead to an elevated pulmonary "capillary" pressure and pulmonary edema, even in the presence of a high pulmonary arteriolar resistance.

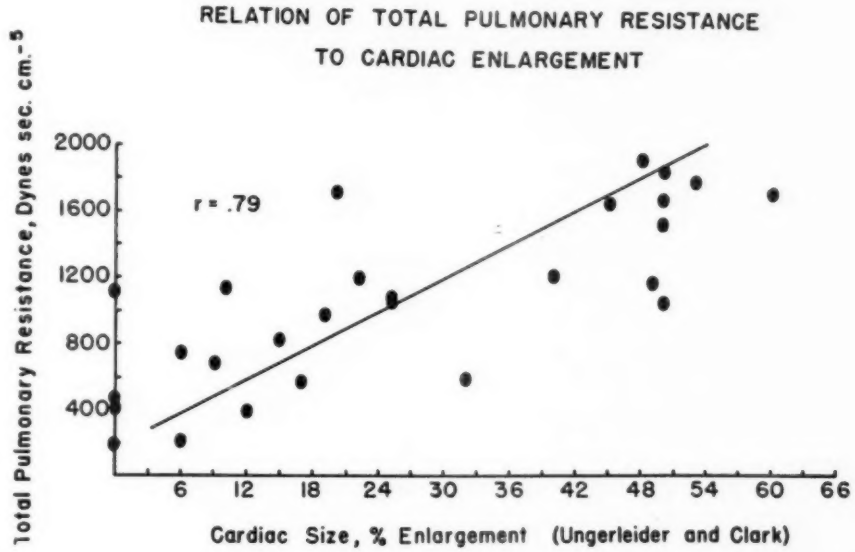

Fig. 5.—The percentage of cardiac enlargement, determined from chest films by the standards of Ungerleider and Clark,[18] is plotted against total pulmonary resistance, the additive result of the resistances of the mitral valve and the pulmonary vasculature. The graph is based on twenty-seven patients as accurate determination of the transverse diameter of the heart was impossible in three cases.

Cardiac Enlargement.—Seventeen patients (Fig. 4, upper left) had cardiac enlargement of 20 per cent or more by the standards of Ungerleider and Clark.[18] Sixteen of these had valve areas of 1.0 cm.^{2} or below. This finding appears to represent the combined effect of a narrow mitral valve and a high pulmonary resistance on the right ventricle, as indicated by the concentration of points about the horizontal asymptote in Fig. 4 (upper left) and the significant linear correlation that exists between total pulmonary resistance, which is the additive result of the resistances presented both by the arterioles and by the mitral valve, and the percentage of cardiac enlargement (Fig. 5). With one exception, a patient in whom low voltage only was noted, all these patients had electrocardiographic evidence of right ventricular hypertrophy or right bundle branch block.

Analysis of other clinical features presented by these patients with cardiac enlargement shows that twelve had manifestations of right ventricular failure (edema and hepatomegaly) associated with cardiomegaly. In contrast, hemoptysis occurred in only one patient with a definitely enlarged heart and paroxysmal nocturnal dyspnea in only eight of this group of seventeen. These differences

support the hypothesis that increase of pulmonary arteriolar resistance protects the lung capillaries from hydrostatic pressure at the expense of increasing the burden of the right ventricle and leading to its enlargement.

It is also of interest that of the twelve patients with apical systolic murmurs of Grade 2+ or more, nine were in the group of patients with cardiac enlargement, although, as noted previously, in none was there physiological evidence of mitral insufficiency.

Edema and Hepatomegaly.—The relationship of mitral valve area and pulmonary arteriolar resistance to symptoms of right ventricular failure is shown in Fig. 4. The five patients in whom detectable pitting edema without appreciable hepatomegaly was noted all had valve areas 1.0 cm.^{2} or smaller, as shown in Fig. 4 (lower left). In none of these cases was the edema more than moderate. Aside from the severity of the stenosis, this group was a rather heterogeneous one. Pulmonary arteriolar resistance ranged from 204 to 853 dynes seconds cm.$^{-5}$ but was on the whole slightly increased, averaging 407 dynes seconds cm.$^{-5}$ Physiological response to the obstacle of a tight mitral valve and a variable increase in pulmonary arteriolar resistance was likewise not consistent. Cardiac index was normal in one patient, moderately reduced in two patients, and greatly reduced in two patients. Right auricular pressure similarly was normal in three patients and definitely elevated in two. Clinically, there was also no clear-cut picture, with two patients having grossly enlarged hearts and few paroxysmal respiratory symptoms and three patients having little cardiac enlargement and predominantly respiratory complaints.

The occurrence of hepatomegaly without significant edema is shown in Fig. 4 (upper right). All six patients in whom the liver was felt two or more fingerbreadths below the right costal margin had valve areas of less than 1.0 cm.^{2} The pulmonary arteriolar resistance was moderately increased, ranging from 225 to 769 dynes seconds cm.$^{-5}$, with an average increase of 518 dynes seconds cm.$^{-5}$, somewhat greater than in the preceding group. The cardiac index was normal in one patient, was moderately decreased in three patients, and was greatly decreased in two patients. Right auricular pressure at the time of cardiac catheterization was normal in two patients, at the upper limit of normal in one patient (5 mm. Hg), and definitely elevated in three patients. Clinically also there was no definite pattern, with four patients having enlarged hearts and two having no cardiac enlargement but prominent respiratory symptoms with frequent hemoptyses.

The patients with both hepatomegaly and edema (Fig. 4, lower right), unlike those having only one of these findings, formed a relatively homogeneous group. All six had valve areas smaller than 1.0 cm.^{2} Five of them fell into the group with extreme elevations of pulmonary arteriolar resistance, ranging from 950 to 1,660 dynes seconds cm.$^{-5}$ Cardiac index was depressed in every case, being 2.0 L. per minute per square meter or less in all patients, and right auricular pressure was elevated in each one, being above 14 mm. Hg in four. Clinically, this group represented the opposite pole from those patients who had frequent hemoptyses. Cardiac enlargement was massive in five cases, and paroxysmal respiratory symptoms had been displaced by signs of peripheral failure as the leading feature in the illness of these patients.

Auricular Fibrillation.—Auricular fibrillation was present in nine patients. All, as shown in Fig. 6 (lower middle), had valve areas smaller than 1.0 cm.^{2} However, since catheterization was not done in patients with auricular fibrillation unless operation was contemplated, the correlation of auricular fibrillation with severity of stenosis may not reflect the occurrence of this arrhythmia in unselected cases of mitral stenosis.

In all nine patients there was evidence of left auricular enlargement. In one this enlargement was graded as slight, in four as moderate, and in four as marked. The elevation of pulmonary arteriolar resistance was quite variable, as was the clinical picture. However, three of the patients did fall into the group with high pulmonary arteriolar resistances, enlarged hearts, and signs of peripheral congestion. All but one were disabled by exertional dyspnea, and eight had evidence of right ventricular hypertrophy or right bundle branch block by electrocardiogram.

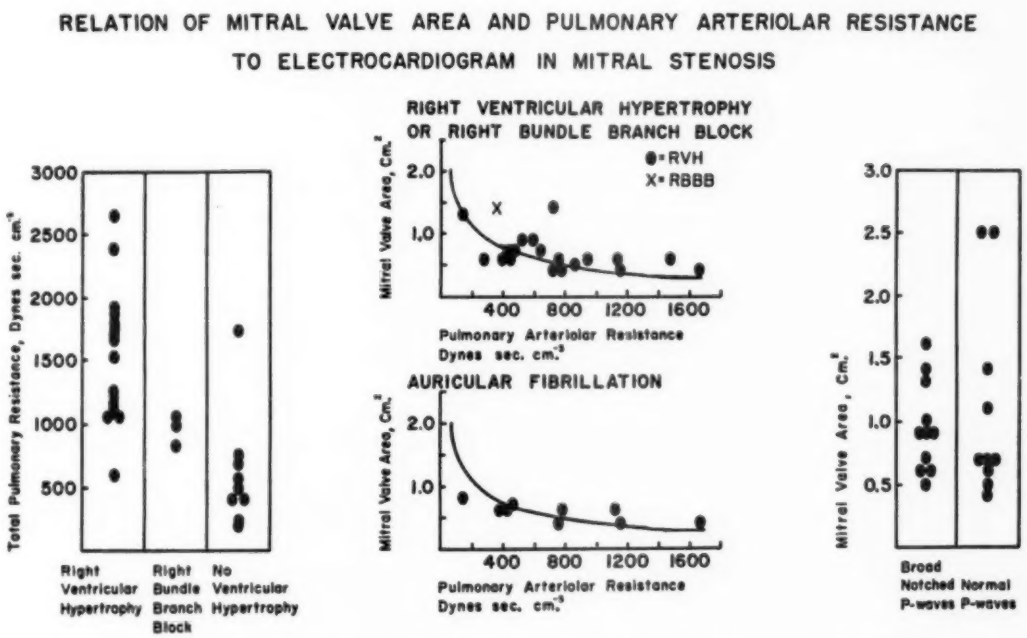

Fig. 6.—In the center are plotted patients having right ventricular hypertrophy or right bundle branch block and auricular fibrillation against the curve relating mitral valve area to pulmonary arteriolar resistance. Note again the grouping of these findings in patients with valve areas below 1.0 cm.^{2} On the left, note the relatively sharp threshold for the electrocardiographic detection of right ventricular hypertrophy at a total pulmonary resistance of 1,000 dynes seconds cm.$^{-5}$ On the right is shown the random distribution of abnormal P waves when plotted against mitral valve area.

Right Ventricular Hypertrophy.—The electrocardiogram, which included unipolar extremity and precordial leads, was interpreted as showing right ventricular hypertrophy in eighteen patients and right bundle branch block in six patients. In three cases they coexisted. When these twenty-one patients were plotted in relation to mitral valve area and pulmonary arteriolar resistance, as in Fig. 6 (upper middle), nineteen were found to have valve areas smaller than

1.0 cm.^{2} The tendency of these points to cluster about the horizontal asymptote suggests that pulmonary arteriolar resistance, as well as the severity of the stenosis, affects the electrocardiographic picture.

In Fig. 6 (left) the distribution of right ventricular hypertrophy is plotted against the total pulmonary resistance, which is a measure of the resistance offered by both the stenosed mitral valve and the narrowed pulmonary arteries. Eighteen of the twenty-one patients with these electrocardiographic abnormalities had total pulmonary resistances of 1,000 dynes seconds cm.$^{-5}$ or greater, and only one patient with a total pulmonary resistance of greater than 1,000 dynes seconds cm.$^{-5}$ failed to show this abnormality. Thus, like roentgenological evidence of cardiac enlargement, electrocardiographic changes diagnostic of right ventricular hypertrophy are a function of both mitral valve area and pulmonary arteriolar resistance. A value of 1,000 dynes seconds cm.$^{-5}$ for the total pulmonary resistance appears to represent a relatively definite threshold for the development of this condition.

In studies done before the wide use of precordial electrocardiography and the elaboration of criteria for the diagnosis of right ventricular hypertrophy by Wilson and associates,[21] Berliner and Master[22] observed that right ventricular preponderance was seen only in buttonhole mitral stenosis and that the tighter the stenosis, the more definite was the evidence of preponderance. In more recent work, Rasmussen and Nyhus[23] have noted the correlation of right bundle branch block with advanced mitral disease and, as judged by cardiac enlargement and by serial electrocardiograms, they have established that it is a late and sequential change in mitral disease. The present study tends to confirm these observations and at the same time delimit the magnitude of anatomical change which is reflected in detectable electrocardiographic abnormality.

P-Wave Changes.—Of the twenty-one patients with normal sinus rhythm, eleven were noted to have high or notched P waves in the electrocardiogram, while ten did not have this finding (Fig. 6, right). Those having abnormal findings had an average valve area of 0.9 cm.^{2}, and those who did not had an average valve area of 1.1 cm.^{2} The accompanying finding of right ventricular hypertrophy, however, was more common in those in whom abnormal P waves were described, occurring in nine patients in this class as against four in those in whom no change in the P wave was noted. Other differences between the two groups are not striking. Elevations of pulmonary arteriolar resistance were comparable. The incidence of cardiac enlargement was approximately the same as was the finding of a moderate or marked dilatation of the left auricle, this finding being present in ten of eleven with abnormal P waves and in nine of ten with normal P waves. From these physiological studies, then, the relation of abnormal P waves to the severity of the stenosis and the degree of pulmonary arteriolar obstruction remains ambiguous.

Left Auricular Dilatation.—Left auricular dilatation was graded at fluoroscopic examination as "slight," "moderate," and "marked," and the presence of systolic expansion of the left auricle was noted. In three patients the dilatation was "slight," in fifteen it was "moderate," and in twelve it was "marked." The relation of auricular dilatation to mitral valve area and pulmonary arteriolar resistance is shown in Fig. 7 (lower).

It will be noted that all of the patients had auricular dilatation of some degree, for such dilatation, as Sosman[24] pointed out, is found even in relatively mild degrees of mitral stenosis, often without symptoms or other clinical manifestations of disease. The number of patients with dilatation graded "slight" is too

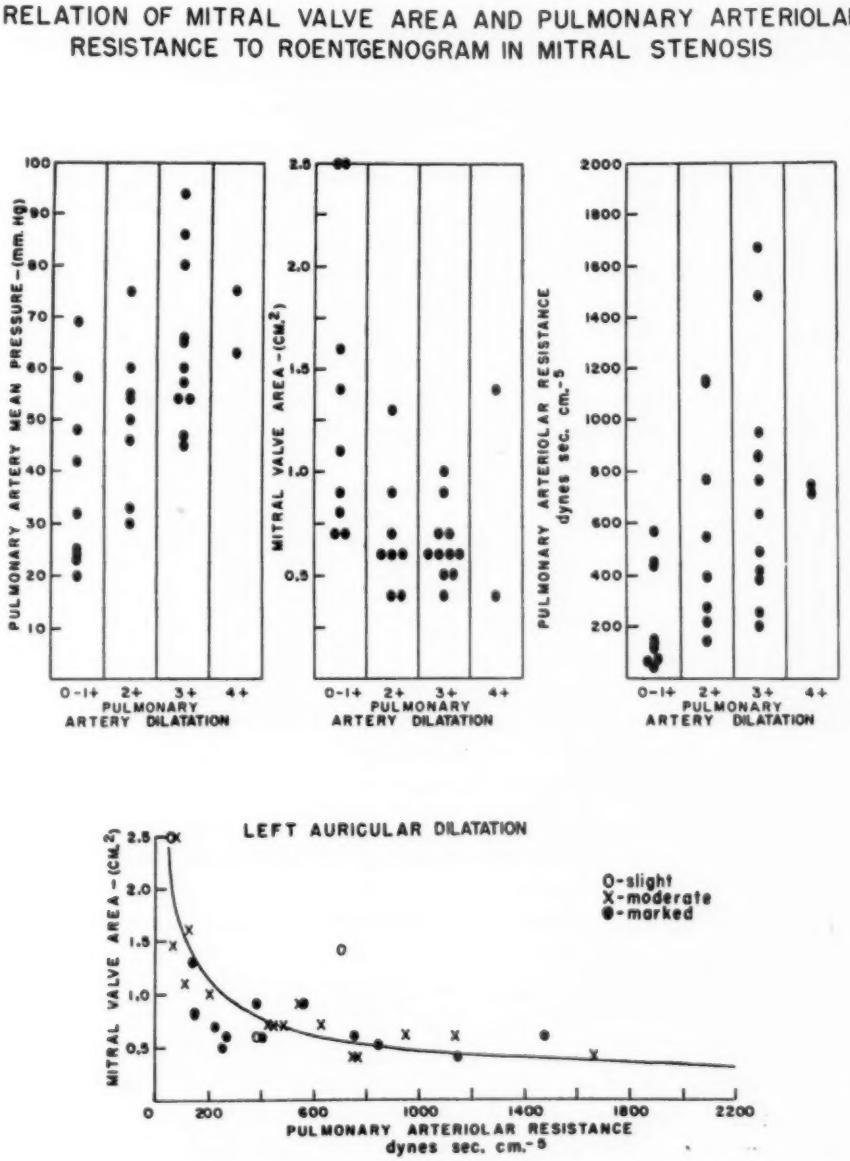

Fig. 7.—In the upper figures, pulmonary artery dilatation is classified by the standards of Healey and co-workers.[27] Note the increase of dilatation with increasing pulmonary artery pressure and the less striking relations to narrow mitral valves and increasing pulmonary arteriolar resistance. Below, three grades of left auricular dilatation are plotted against the curve relating mitral valve area to pulmonary arteriolar resistance.

small to enable definite conclusions as to the level of stenosis at which "slight" dilatation becomes "moderate" or "marked."

An attempt to relate the observed dilatation to auricular pressure, which in turn is largely controlled by the valve area and the arteriolar resistance, is difficult, since it is probable that increased pressure is not the sole factor in the pathogenesis of atrial dilatation. Schwedel,[25] discussing this problem, noted that the dilatation found in left ventricular failure with increased atrial pressure is rarely of the same magnitude as that seen in mitral stenosis. He cited the chronicity of mitral disease and the influence of rheumatic involvement of the atrial myocardium as possible reasons for this difference. It is of interest, however, in view of the role of the pulmonary arteriolar resistance in protecting the postarteriolar bed from sudden increases in hydrostatic pressure, that many of those with "marked" dilatation have the combination of slight increase in pulmonary arteriolar resistance and a narrow (1.0 cm.^{2} or less) valve, while, conversely, many of those with a high pulmonary arteriolar resistance and a narrow valve had a left auricle only "moderately" dilated.

It is also worth noting that in these patients auricular dilatation and generalized cardiac enlargement to some extent parallel one another, as indicated by the fact that only one of the patients with "slight" dilatation had enlargement of 20 per cent or more, while eight of fifteen with "moderate" dilatation presented this finding as did eight of twelve with "marked" dilatation.

The presence of systolic expansion of the left auricle was noted in six of the thirty patients and was equivocally present in two others (Table I). In none was this believed to be the result of mitral insufficiency, as the V-wave height in the pulmonary "capillary" tracing was not increased in any patient. In three, the absence of regurgitation was confirmed by palpation of the valve at operation,* and in two additional patients there was no significant apical systolic murmur. There is no doubt, however, that this sign is frequently observed in mitral insufficiency,[26] and it has been seen in ten of fifteen patients presenting the physiological criteria of mitral insufficiency.[16]

Pulmonary Artery Dilatation.—The roentgenographic appearance of the pulmonary artery was graded from 0 to 4+ by the standards of Healey and associates.[27] In congenital heart disease and in a small series of patients with mitral stenosis, they found that either increased pressure or increased flow resulted in a dilatation proportional to the increase. As will be seen from Fig. 7 (upper left), this relation holds in general for this series of thirty patients, although there is some overlapping.

The increased pressure in the pulmonary artery is necessitated by the narrowed mitral valve and the increase in pulmonary arteriolar resistance. The distribution of pulmonary artery dilatation by valve area and by the magnitude of pulmonary arteriolar resistance is shown in Fig. 7 (upper middle and upper right).

While the valve areas ranged from 0.7 to 2.5 cm.^{2} in the group with 0 to 1+ dilatation, pulmonary arteriolar resistances were at most moderately elevated.

*By Dr. Dwight E. Harken.

Those with relatively wide valves (1.4 cm.^{2}) were asymptomatic, but those with narrower valves had hemoptyses as a prominent symptom in three cases.

In the eight patients in whom dilatation was graded 2+, valve areas were on the whole narrower and pulmonary arteriolar resistances higher than in the preceding group, although there was considerable overlap. Differences between this group and those in whom dilatation was graded 3+ (eleven patients) and 4+ (two patients) were not clear-cut. Thus it was seen that an appreciably dilated pulmonary artery usually indicates an elevated pulmonary arteriolar resistance and a narrow mitral valve, but relatively little dilatation may be seen with a narrow valve when there is no accompanying increase of arteriolar resistance.

DISCUSSION

When the mitral valve is narrowed by disease, the circulation compensates by the adjustment of pressure and flow across the mitral valve and by the development of increased vascular resistance in the lungs.

As the mitral valve becomes smaller, flow through the valve will be reduced if left auricular pressure remains the same, and, conversely, pressure in the left auricle must rise if blood flow is to remain the same.[6] The factors which limit compensation in this way are (1) the development of pulmonary edema if the pressure in the pulmonary capillaries, which must be greater than the left auricular pressure, exceeds the osmotic pressure of the plasma protein[11] and (2) bodily demands for a certain minimum quantity of oxygen which can be supplied only by a certain minimum quantity of blood flow. However, compensation for the stenosed valve by alteration of pressure and flow alone is effective when the stenosis is mild (as in patients J. D., F. C., J. F., L. B., and J. M.), for in these patients cardiac outputs within the normal range can be secured with left auricular pressures well below the osmotic pressure of the plasma proteins.[6] While the demands of exercise may cause a marked rise in left auricular pressure[17] and thus be productive of symptoms, the resting equilibrium is such that these patients are little incapacitated.

As the stenosis increases toward a valve of 1.0 cm.^{2} or smaller, a left auricular pressure approaching plasma osmotic pressure (approximately 25 mm. Hg) becomes necessary to support a barely normal resting flow.[11] This point, when the valve area is one-fourth or less the normal valve, is a critical one in the course of the disease because tolerable left auricular pressures and normal cardiac output can no longer exist together. Hence, at this point the clinical manifestations of severe mitral disease will become evident. The clinical picture in a given patient, however, will depend on a third compensatory mechanism—an increase in pulmonary vascular resistance.

A resting equilibrium requiring such a high pressure apparently is the stimulus for the development of increased vascular resistance in the lungs.[7] This resistance increases along a hyperbolic curve as the valve grows smaller than 1.0 cm.^{2} By decreasing cardiac output, pulmonary arteriolar resistance shifts the pressure-flow equilibrium toward a lower left auricular pressure. This increased vascular resistance is a physiological counterpart of the anatomical changes ob-

served in the small pulmonary arteries.[1,28] Since it is not appreciably changed by brief exercise,[17] it apparently represents a relatively constant day-to-day obstacle against which the right ventricle must work. There is, however, evidence from histological study[28] and from physiological observations following mitral valvuloplasty[29] that some of this increased resistance may be on the basis of vasoconstriction in addition to organic narrowing of the vessel.

The pulmonary arteriolar resistance is of importance physiologically and, in turn, clinically in two ways. First, it is a highly effective damper to sudden surges of output by the right ventricle. Without this high resistance the pulmonary capillaries are exposed directly to increased right ventricular discharge of blood,[7] since egress of blood from the lungs is obstructed by the narrow mitral valve. When the arteriolar resistance is high, however, right ventricular output is decreased and sudden surges of blood to the capillary bed do not occur.[6] Second, the higher the resistance, the greater the strain under which the right ventricle works. A high resistance, then, will lead to muscular hypertrophy, chamber dilatation, and eventually right ventricular failure.

Thus the clinical manifestations of mitral disease are considerably modified by the magnitude of the pulmonary arteriolar resistance. Ideally, the increase in resistance would be just great enough to protect the pulmonary capillaries from sudden congestion, but not so great as to cause failure of the right ventricle. Alternatively, however, this resistance may be increased too slightly to reduce right ventricular output effectively and symptoms depending on pulmonary congestion will dominate the clinical picture, or the increase in resistance will exceed the pumping ability of the right ventricle and symptoms dependent on its failure will be apparent.

Physiologically then, patients with mitral stenosis can be divided into four groups based on the two factors, mitral valve area and pulmonary arteriolar resistance. The first group consists of those with a stenosis mild enough to enable compensation by alterations in pressure and flow alone. The second, third, and fourth groups are made up of those with valve areas of 1.0 cm.^{2} and under, where compensation in this way is no longer possible and increases in pulmonary arteriolar resistance are, respectively, too slight to diminish pulmonary congestion, just sufficient to mitigate episodes of congestion, or so great that the right ventricle fails. When the patients in this series are divided by such a physiological classification, those patients in each group are found to have many clinical features in common and thus to form clinical patterns similar to the physiological patterns. As might be expected, there is some overlapping, and a few cases do not fit well into these divisions.

Group I consisted of four patients (J. D., F. C., J. F., and L. B.). The valve area in all cases was 1.3 cm.^{2} or above, and the pulmonary arteriolar resistance did not exceed 135 dynes seconds cm.$^{-5}$ The only symptom noted was mild exertional dyspnea. Neither cardiac enlargement nor signs of right ventricular failure occurred in this group.

Group II consisted of ten patients (Gr., N. W., R. C., L. T., B. A., S. V., M.T., E. S., J. G., and D. K.). These patients had comparatively narrow valve orifices (0.5 to 1.1 cm.^{2}) and relatively slight elevation of pulmonary arteriolar

resistance (up to 569 dynes seconds cm.$^{-5}$). In this group respiratory symptoms predominated with severe exertional dyspnea, frequent paroxysmal nocturnal dyspnea, hemoptyses in one-half the cases, and recurrent bouts of pulmonary edema. Right ventricular hypertrophy or right bundle branch block was found in six, but appreciable cardiac enlargement, in each only moderate, occurred in only three. None was in frank right ventricular failure.

Group III consisted of five patients (T. C., L. L., McL., F. M., and D. V.). These individuals had severe stenosis (0.4 to 0.7 cm.^{2}) and moderate elevations of pulmonary arteriolar resistance (488 to 853 dynes seconds cm.$^{-5}$). This degree of resistance produced a balance between cardiac output and pulmonary pressures such that the patient could work at light occupation without severe dyspnea, be relatively free of paroxysmal respiratory symptoms, and yet have few signs of peripheral failure. Weakness, tiredness, and easy fatigability were prominent symptoms in this group. The right ventricle, however, bearing the brunt of this increased resistance as well as the load imposed by severe stenosis, tended to be massively enlarged with cardiac size about 50 per cent above normal in four of these patients.

Group IV was made up of six patients (W. F., N. L., M. G., M. M., H. W., and McG.). The valve areas were quite narrow (0.4 to 0.6 cm.^{2}), and the pulmonary arteriolar resistance was markedly elevated (770 to 1,660 dynes seconds cm.$^{-5}$). Clinically, this group had severe exertional dyspnea, grossly enlarged hearts, peripheral edema, and hepatomegaly. Hemoptyses were not seen in this group, and bouts of pulmonary edema were rare. The incapacitating dyspnea may be related to the high pulmonary artery pressure or to the pulmonary vascular process, since similar dyspnea has been observed in chronic cor pulmonale in which no abnormalities in blood composition or in ventilation could be demonstrated.[15]

As is true in any complicated disease process, there are bound to be certain cases which differ from the general patterns that can be delimited. Of the thirty patients in this study, twenty-five fitted into the groups discussed. Five patients, however, presented important differences and will be discussed briefly here.

Patient J. M. had a relatively wide valve (1.3 cm.^{2}) and a slight elevation of pulmonary arteriolar resistance (145 dynes seconds cm.$^{-5}$). There was, however, considerable cardiac enlargement (32 per cent above normal), but the only symptom was mild dyspnea. This patient was the youngest (22 years) in this series, and the possibility of smoldering rheumatic fever cannot be excluded with certainty.

Patient L. C. had a relatively wide valve (1.4 cm.^{2}), but a very high pulmonary arteriolar resistance (711 dynes seconds cm.$^{-5}$). This patient, however, had predominantly respiratory symptoms, hemoptyses, paroxysmal nocturnal dyspnea, and frequent bouts of acute pulmonary edema.

Patient M.B. was severely dyspneic and had hepatomegaly and edema, but unlike other patients with this combination of symptoms had a low pulmonary arteriolar resistance (150 dynes seconds cm.$^{-5}$) and little cardiac enlargement (17 per cent above normal).

Patient E. D., while having a narrow mitral valve (0.6 cm.^{2}) and a comparatively slight elevation of pulmonary arteriolar resistance (411 dynes seconds cm.$^{-5}$), had few paroxysmal respiratory symptoms, possibly because she led a very inactive protected life, but she did have an enlarged heart (40 per cent above normal) and a palpable liver.

Patient R. W., like E. D., had a narrow valve (0.6 $cm.^2$), a low pulmonary arteriolar resistance (274 dynes seconds $cm.^{-5}$), and an enlarged heart (50 per cent above normal). There was mild peripheral edema. In neither case was there evidence of rheumatic fever, either from clinical findings or from examination of the auricular appendage removed at operation, to explain the cardiomegaly.

Despite such exceptions, the observations presented here clarify to some extent the variability of symptoms in mitral stenosis and explain in terms of pressure-flow relationships and pulmonary arteriolar resistances why one patient may have severe pulmonary symptoms while another, with little difference in the degree of stenosis, may present primarily signs of right ventricular failure. It also explains why, in some patients, there is a period of relative freedom from dyspnea after a period of severe respiratory distress. This has been attributed to right ventricular failure. Our observations in adult patients indicate that the probable cause is increase of the pulmonary arteriolar resistance with limitation of right ventricular output and, hence, lessening of pulmonary congestion. Indeed, in our cases when there is right ventricular failure, as indicated by hepatomegaly and edema, there is often incapacitating dyspnea which is not apparently on the basis of pulmonary edema but is related in some way to the high resistance itself, as discussed previously.

Further, these clinical studies confirm the deduction drawn from physiological analysis[6] that a valve area of 1.0 $cm.^2$ (from one-quarter to one-sixth normal) represents a critical narrowing of the mitral valve. Physiologically, at this point a high left atrial pressure becomes necessary, cardiac output begins to fall, and pulmonary arteriolar resistance increases. Clinically, of eight manifestations of advanced mitral stenosis—disabling exertional dyspnea, hepatomegaly, edema, cardiac enlargement (20 per cent or more), left auricular dilatation ("moderate" or "marked"), pulmonary artery dilatation (2+ or more), right ventricular hypertrophy or right bundle branch block by electrocardiogram, and auricular fibrillation—no patient with a valve area of 1.0 $cm.^2$ or less had fewer than four, while only one patient with a larger valve area had this many.

SUMMARY

1. The area of the mitral valve and the degree of pulmonary vascular disease have been calculated from physiological data in thirty patients with pure mitral stenosis without evidence of active rheumatic carditis.

2. From a hydraulic point of view, a valve area of 1.0 $cm.^2$, one-quarter to one-sixth normal, appears to be a critical one, for at that level of stenosis the pressure head needed to maintain a normal cardiac output approaches the plasma osmotic pressure.

3. Probably from the stimulus of an increased pulmonary "capillary" pressure, a variable degree of vascular obstruction develops in patients when the mitral valve area becomes reduced to about 1.0 $cm.^2$ or smaller. This results in a lower cardiac output, which may protect the capillary bed from sudden increases in pressure.

4. The clinical picture in mitral stenosis can be explained in a large measure by the interplay of the degree of stenosis with the degree of pulmonary vascular obstruction.

5. The combination of a narrow valve with only a slight increase in pulmonary arteriolar resistance is associated with predominantly respiratory symptoms, exertional dyspnea, hemoptysis, and paroxysmal nocturnal dyspnea, the right ventricle not becoming dilated.

6. The effect of a narrow valve and a high pulmonary arteriolar resistance appears to be additive in causing electrocardiographic evidence of right ventricular hypertrophy and roentgenographic signs of cardiac enlargement.

7. The combination of a narrow valve and great increases in pulmonary arteriolar resistance is associated with severe dyspnea, cardiac enlargement, and signs of right ventricular failure.

8. Most patients with mitral stenosis can be divided into four general categories by their signs, symptoms, and physiological adjustments.

The authors are indebted to Dr. Merrill C. Sosman and his staff for roentgenographic examinations, to Dr. Harold D. Levine and associates for electrocardiographic interpretations, and to Dr. James L. Whittenberger for the use of the facilities of his laboratory.

The technical services of Miss Libby Servello and the secretarial aid of Miss Barbara Johnson are likewise acknowledged.

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MORPHOLOGY OF THE UNIPOLAR LEADS RECORDED AT THE SEPTAL SURFACES. ITS APPLICATION TO THE DIAGNOSIS OF LEFT BUNDLE BRANCH BLOCK COMPLICATED BY MYOCARDIAL INFARCTION

Dedicated to Carl J. Wiggers

DEMETRIO SODI-PALLARES, M.D., AND MARÍA ISABEL RODRÍGUEZ, M.D.

MEXICO, D. F.

GENERALLY speaking, up to the present time, electrocardiographic information concerning the anatomical condition of the interventricular septum has been quite meager. In some forms of myocardial infarction, it is possible to say that necrosis has extended to the septum, and it can even be determined if the septal infarct is slight or massive. The diagnosis of anteroseptal infarction frequently can be established, and several cases have been reported in which the electrocardiographic diagnosis of extensive destruction of the septum was made and confirmed.

More frequently, some functional alterations are described located at the interventricular septum. Complete or incomplete bundle branch blocks and septal extrasystoles may or may not be related to myocardial damage at the site we are referring to.

Probably, the interventricular septum is seldom mentioned during electrocardiographic interpretation because little is known of the sequence of the activation process in the septal muscle fibers and the morphology of unipolar leads in each of the surfaces of this structure.

In the majority of unipolar leads (excluding intraventricular leads) the solid angle englobed by the exploring electrode includes important areas of the epicardial surface of the heart and apparently very little or none of the interventricular septum, at least in a direct fashion. Yet extensive transmural infarction forms an electric window, and the electrode may thus be oriented to any septal surface. Also, when the activation has not reached the free walls and the tissue of these is not yet activated, the analysis of the solid angle must be referred to the septum and not to the epicardial surfaces of the heart.

There is no doubt that knowledge of the potential variations at the endocardial surfaces of the septum will assist in better interpretations of electrocardiographic tracings, especially when electrical windows are present and the exploring electrode is oriented directly toward these surfaces.

Recently, Sodi-Pallares and co-workers[1] were able to place special electrodes on the septal surfaces of the heart of the dog. The sites where they were placed were carefully controlled at autopsy. In the majority of instances the electrodes

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produced a certain degree of injury, but after a reasonable period of time RS-T displacements due to this injury disappeared, and the morphology of the unipolar leads in different sites of the endocardial surfaces of the interventricular septum could be easily recognized.

Occasionally, the sensitive portion of the electrode did not reach the surface of the septum, and unipolar tracings were thus obtained in the substance rather than on the surface of the septal muscle. In these cases also, the injury produced by the electrode disappeared after a short time. These latter tracings are unimportant under normal conditions, since the electrical phenomenon must be referred to the differences existing between the two surfaces, regardless of the events that took place within the septum, just as in the free ventricular walls. However, when scar tissue which, from the electrical standpoint, is dead invades an extensive portion of the surface of the septum, the undamaged portion of muscle substance contiguous to the dead tissue will now form a part of the septal surface; this must be taken into consideration in the interpretation of the tracings. Some examples which will be given later will illustrate these views.

The sketches of Figs. 1, 2, and 3 were obtained from the paper[1] previously mentioned. They show the morphology of unipolar leads at different levels of the septal surfaces. The T wave was not taken into consideration because of the lability of the process of repolarization under the experimental conditions described.

One must not forget, as was proved in a previous paper,[1] that there are areas of the right septal surface that belong to the left ventricle where it is possible to delay the arrival of the wave of activation by means of percussion or section of the left bundle. These portions are proximal to the trabecular zone in the majority of cases and are represented in the drawings by dotted areas, as is the rest of the left ventricular muscle mass. On the other hand, the areas corresponding to the right ventricle are represented by lines. It is not necessarily true that the left ventricular fibers form part of the right septal surface near the trabecular portion only; they may form a part of the right septal surface at even higher levels, depending on the level at which the anatomical section is made.[1]

MORPHOLOGY OF THE UNIPOLAR LEADS ON THE SEPTAL SURFACES OF THE NORMAL HEART OF THE DOG

Right Septal Surface.—At the lower portions formed by the right ventricle, the complexes are of the rS type (Fig. 1, *a*). At the low or middle portions formed by the left ventricle, the complexes are also of the rS type (Fig. 1, *b*), but the intrinsic deflection is registered somewhat sooner than that corresponding to the right ventricular complexes. At the higher portions belonging to the right ventricle, the complexes are of the RS or Qr type (Fig. 1, *c*) with a delayed intrinsic deflection as compared with the previous one. These morphologies also suggest that, at least on this surface, the process of activation develops from below upward. The possible explanation of the Qr type of tracings at the higher levels has been mentioned previously.[1]

Left Septal Surface.—This belongs to the left ventricle, and at all levels the complexes are negative and of the QS type (Fig. 1, *d*, *e*, *f*). Yet at lower levels, proximal to the heart apex, rS type complexes may be registered (Fig. 1, *d*).

MORPHOLOGY OF THE UNIPOLAR LEADS OVER THE SEPTAL SURFACES OF THE HEART OF THE DOG IN CASES OF LEFT BUNDLE BRANCH BLOCK

Right Septal Surface.—At the low portions that belong to the right ventricle, the complexes are of the QS or rS type with a wide S wave and frequently with

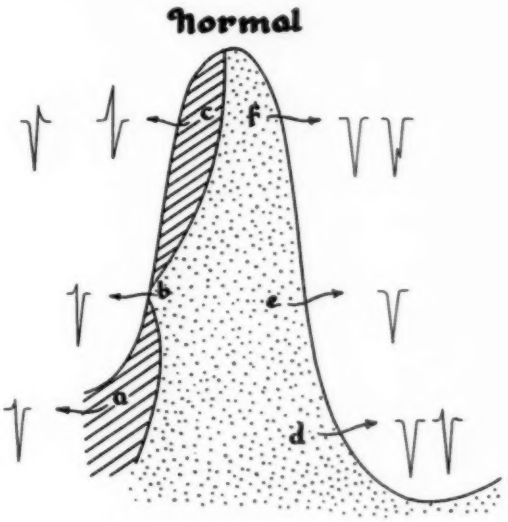

Fig. 1.—Form of unipolar tracings obtained from the surfaces of the interventricular septum of the normal dog.

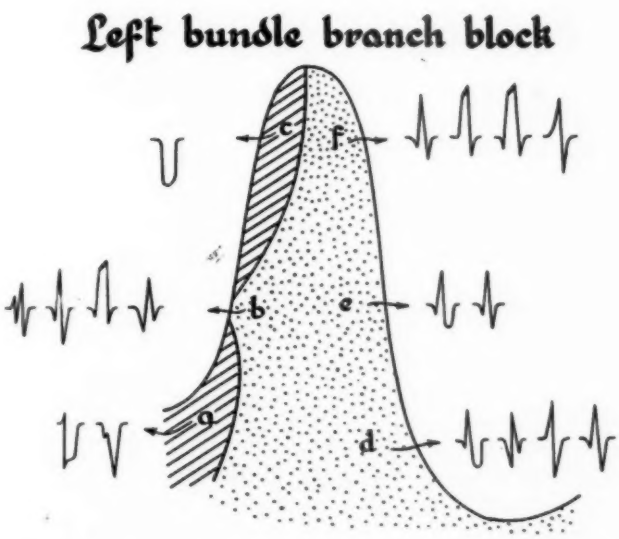

Fig. 2.—Form of unipolar tracings obtained from the surfaces of the interventricular septum of dogs which have had the left bundle branch cut.

notchings and slurrings (Fig. 2, *a*). These tracings are similar to those obtained in the right ventricular cavity with the same variety of bundle branch block.

At middle levels belonging to the left ventricle, the complexes may be of the rsRS, qRS, qRs, and QRs types (Fig. 2, *b*) with notchings and slurrings, especially of the positive portion of the complex. The wave of activation arrives very late at these places as compared with the arrival at adjacent portions of the septum.

At upper levels formed by the right ventricle, the complexes are of the QS type, similar to those of the lower levels (Fig. 2, *c*).

Left Septal Surface.—The complexes are similar at any level considered, and the morphology may be of different types: qRS with great duration of S, qRS with a shorter duration of S, QRs, qRs, and RS. Unipolar tracings recorded within the substance of the septal ventricular muscle have a similar morphology, and they also belong to the left ventricle.

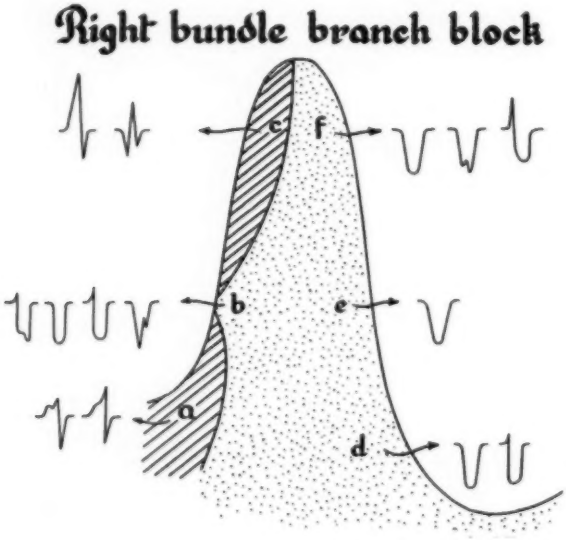

Fig. 3.—Same as Fig. 2, except the right branch has been cut instead of the left.

MORPHOLOGY OF THE UNIPOLAR LEADS AT THE SEPTAL SURFACES OF THE HEART OF THE DOG IN CASES OF RIGHT BUNDLE BRANCH BLOCK

Right Septal Surface.—At lower levels belonging to the right ventricle (Fig. 3, *a*), complexes are of the RS type with a positive deflection which is wide and slurred and a delayed intrinsic deflection.

In middle portions belonging to the left ventricle, the complexes are essentially negative (Fig. 3, *b*), of the QS, rS types with an early inscription of the intrinsic deflection and a negative wave of great duration, often notched and slurred.

At high levels formed by the right ventricle, the complexes are of the RS or QRs type with a delayed intrinsic deflection.

Left Septal Surface.—The complexes are similar at any level considered; they are of the QS or rS type with a negative wave of great duration and with an early inscription of the intrinsic deflection.

LEFT INTRAVENTRICULAR POTENTIAL

The morphology of the tracings obtained in the left ventricular cavity is the same in human hearts as in the dog's heart. Under normal conditions the ventricular complex is entirely negative and of the QS type.[2,3] When there is an incomplete or complete left bundle branch block, the complexes are of the RS type.[3]

The exploring electrode within the cavity is oriented to extensive areas of the left septal surface. We have seen that on this surface, in the presence of left bundle branch block, the complexes are of the RS type, or they may show a slight initial negativity (qRS, qRs) or even a larger initial negative deflection (QRs). Nevertheless, since the intracavity tracing is of the RS type, one must admit that the left septal areas which show similar complexes, that is, RS, are more extensive than other areas with other types of complexes.

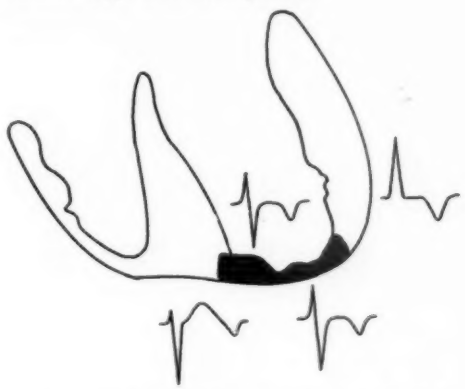

Fig. 4.—Schema to explain the tracings obtained in the precordial leads in a case similar to that in Fig. 5, with anterolateral infarction plus incomplete left bundle branch block.

One can also say that if these regions where an initial positivity is inscribed are destroyed by myocardial infarction, the areas which give a tracing with a Q wave will be predominant, and a similar potential will be registered within the ventricular cavity. In some cases, which will be described later, it will be seen that this does occur.

The morphology we have just described may explain some of the abnormalities found in tracings with myocardial infarction plus complete or incomplete left bundle branch block.

COMPLETE OR INCOMPLETE LEFT BUNDLE BRANCH BLOCK PLUS INFARCTION OF THE ANTEROLATERAL PORTION OF THE FREE WALL OF THE LEFT VENTRICLE WITH LITTLE OR NO INVOLVEMENT OF THE SEPTUM

This conduction disorder causes complexes of the RS or rS type within the eft ventricular cavity. The T wave is negative in the majority of instances.

Occasionally, it is positive.[3] If a transmural infarction of the left ventricular wall appears at the same time, the intracavity potential will be transmitted to the electrode (Fig. 4).

Generally, these cases are difficult to diagnose, and one must think of the possibility of such a disorder when there are data which suggest complete or incomplete left bundle branch block with RS complexes and a negative T wave of the coronary type in V_5 and V_6, especially in patients who have had a history suggestive of myocardial infarction. The fact that no electrocardiographic evidence of dead tissue (Q wave) appears when the T and RS-T changes are evident must suggest the possibility of an infarct with an added block of the left branch.

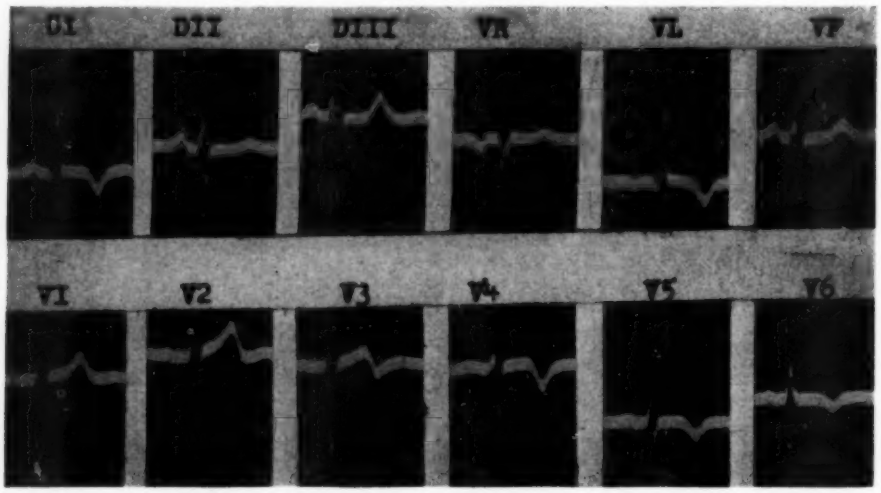

Fig. 5.—Tracing suggestive of anterolateral infarction with slight septal invasion plus incomplete left bundle branch block.

Fig. 5 shows an electrocardiogram from a man 50 years of age who exhibited symptoms highly suggestive of myocardial infarction. In spite of the alterations of T and RS-T in the left precordial leads, a Q wave was not inscribed. Besides, the slurring of the ascending limb of the R wave in V_L and I suggests the presence of an incomplete left bundle branch block.[4] It was thought that a transmural infarct of the left ventricular wall might be present. Autopsy revealed the following data: The heart was large (weight 610 grams), especially the left ventricle. Over the middle and lower thirds of the anterior portion of the free ventricular wall of the left ventricle, there was a whitish zone of irregular shape, poorly limited, measuring 4 by 2 cm. In this area the myocardium was very thin and on section showed numerous whitish areas of fibrous aspect which coalesced to form a large area where no muscular tissue could be elicited. No sclerotic zones were seen at the septum. The study of the coronary circulation with an opaque substance by the method of Schlesinger showed that it was normal at the level of the interventricular septum, but, in contrast, it was very much damaged at the free wall of the left ventricle. Furthermore, it was nonexistent within the infarcted area described previously.

COMPLETE OR INCOMPLETE LEFT BUNDLE BRANCH BLOCK WITH ANTEROLATERAL INFARCTION OF THE FREE WALL OF THE LEFT VENTRICLE AND LOW SEPTAL INVOLVEMENT OF MORE OR LESS EXTENSIVE, BUT NOT MASSIVE, NATURE

One of us has described complexes of the qRs or qRS type in the left precordial leads associated with a complete or incomplete left bundle branch block.[4] The S wave of these complexes is often wide and slurred. For this reason those leads (V_5 and V_6) could suggest by themselves the presence of a right bundle branch block. Nevertheless, exploring points situated farther to the left (V_7 and V_8) or higher in the axilla produced complexes which were characteristic of left bundle branch block.

Fig. 6.—Schema to explain the morphology of the precordial leads in a case similar to that in Fig. 7, with anterolateral infarction with invasion of the lower septum, more or less extensive but not massive, complicated by incomplete left bundle branch block.

The greatest part of the tracings with the characteristics mentioned is associated with infarction of the lower one-third of the interventricular septum and some portion of the free left ventricular wall adjacent to the infarction area of the septum. The qRS and RS complexes, which sometimes are accompanied by a wide and slurred S wave, have their origin in regions of the septum that are not infarcted. In the left ventricular cavity the same complexes may be observed, and, through the transmural infarction of the free wall, they are also found in V_5 and V_6 (Fig. 6). As was previously mentioned, the origin of these complexes is in portions of the septum belonging to the left ventricle; for this reason it must be admitted that the septal infarction is not massive.

In Fig. 7 is shown an electrocardiogram which suggests incomplete left bundle branch block in Leads I and V_L in spite of the presence of a Q wave in these leads. In left precordial leads the complexes are of the qrs type in V_5 and qRs in V_6 with a wide and slurred S wave. Autopsy disclosed an infarcted area involving the lower one-third of the interventricular septum and part of the free wall of the left ventricle. The infarction produced an aneurysm at the apex of the heart. The upper two-thirds of the septum were not involved.

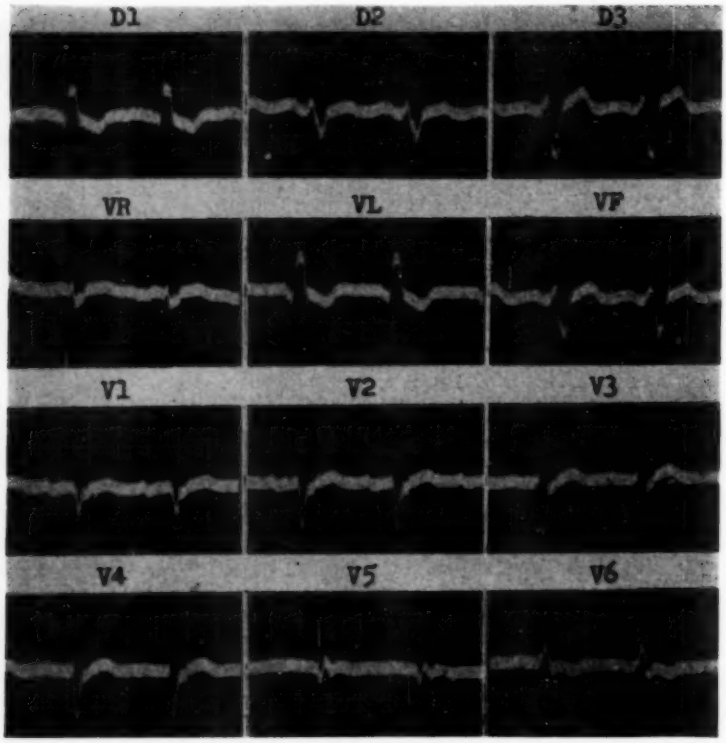

Fig. 7.—Anterolateral infarction with invasion of the lower septum, complicated by incomplete left bundle branch block.

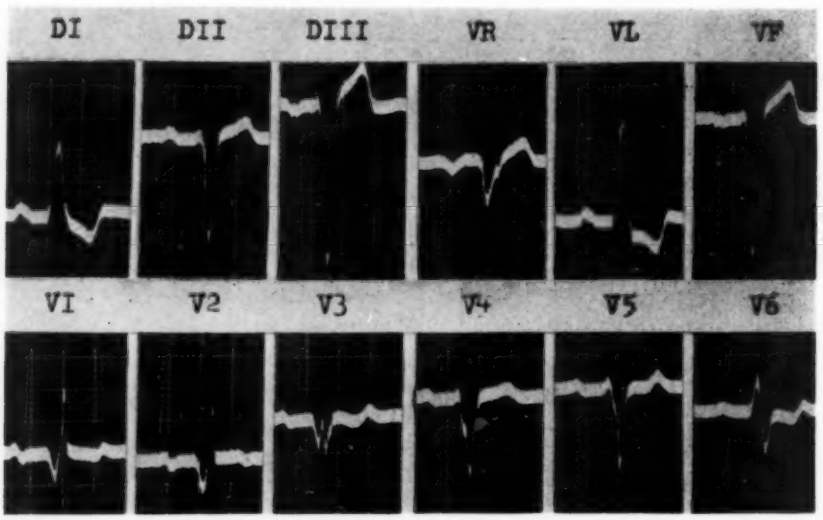

Fig. 8.—Tracing in which the precordial leads erroneously suggest right bundle branch block, but which actually are of left bundle branch block plus anterolateral infarction with invasion of the lower septum.

COMPLETE OR INCOMPLETE BLOCK OF THE LEFT BUNDLE BRANCH WITH PRECORDIAL LEADS THAT ERRONEOUSLY SUGGEST A RIGHT BUNDLE BRANCH BLOCK ASSOCIATED WITH ANTEROLATERAL INFARCTION OF THE FREE WALL OF THE LEFT VENTRICLE AND WITH MORE OR LESS EXTENSIVE, ALTHOUGH NOT MASSIVE, SEPTAL INVOLVEMENT

We have no autopsy proof of this condition, for which reason we will study first the electrocardiographic tracing. Fig. 8 shows an electrocardiogram where the standard and limb leads are suggestive of left bundle branch block. Precordial leads interpreted in the usual way suggest a right bundle branch block (greatly delayed intrinsicoid deflection in V_1 and V_2, S wave wide and slurred in V_5 and V_6) with dead tissue at the anteroseptal level (deep Q wave in V_1, V_2, and V_3).

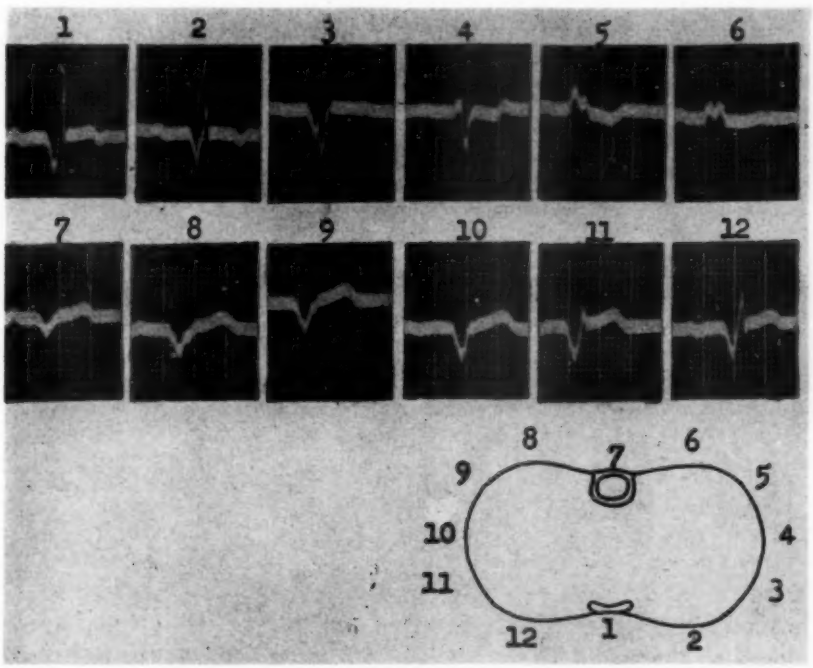

Fig. 9.—Leads taken around the thorax at the level of the third intercostal space from the same case as Fig. 8. These show that left bundle branch block is actually the diagnosis.

Considering the discrepancies existing between the precordial leads on one hand and the standard and limb leads on the other, especially as concerns the interpretation of the type of block, we registered unipolar leads around the thorax at different levels. Fig. 9 shows those obtained in the third intercostal space at the points shown in the adjoining sketch. The circle of tracings taken in the fourth intercostal space was similar. The tracings taken at points *5* and *6* (diagram of the figure) were characteristic of left bundle branch block. All the tracings of the right hemithorax supported the idea that there was no right bundle branch block. Nevertheless, points *11*, *12*, *1*, and *2* were of the Qr or QR type

with a delayed intrinsicoid deflection and could suggest a certain degree of block in some of the subdivisions of the right branch.

We believe, though, that there is another explanation which is more in agreement with the facts and the clinical data (hypertensive patient with symptoms of myocardial infarction). Assume (see Fig. 10) that there is an infarction of the lower portion of the septum which invades to a certain degree both free ventricular walls. The infarct extends then in the septum to portions formed by the right ventricle, and it reaches only partially those formed by the left ventricle. For this reason the left intraventricular potential is that which is found when there is a left bundle branch block; this potential is transmitted through the infarction of the free wall to precordial leads V_5 and V_6 (Fig. 10). On the contrary, Leads V_1 and V_2 have the electrode oriented to portions of the substance of the septum, which now constitutes the surface, where we have described complexes of the qRs type when there is a left block (Fig. 2). The S wave disappears in the right precordial leads because injury is added to the dead tissue. This type of infarction differs from the previous one in the fact that it reaches only partially the lower portion of the septum formed by the left ventricle.

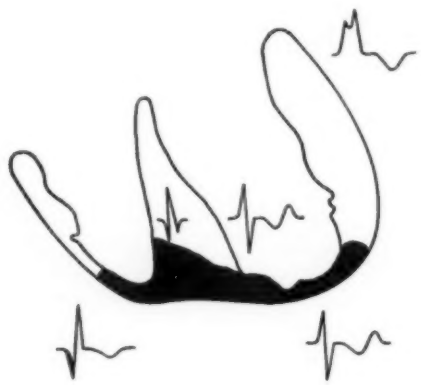

Fig. 10.—Schema to explain the morphology of the precordial leads in the case shown in Figs. 8 and 9.

The case illustrated in Figs. 11, 12, 13, and 14 is quite interesting and probably belongs to the same group. It is of a patient who, at the age of 37 years, during an attack of typhoid fever, showed a clinical picture of myocardial infarction. One of the tracings obtained during this time was characteristic of an extensive anterior infarction with anteroseptal necrosis (Fig. 11) without evidence of bundle branch block. A year later, a new picture of myocardial infarction appeared, and the tracing taken a few hours after the pain (Fig. 12) was characteristic of atrioventricular block with intraventricular block (QRS of 0.15 second duration with an M complex in Leads II, III, and V_F) which we interpreted as probable left bundle branch block. The atrioventricular block disappeared spontaneously but reappeared after an attack of diphtheria which complicated the picture (Fig. 13). In the tracings taken during that time, there was still a certain degree of injury, and Lead V_6 was strongly suggestive of left bundle branch block, thus confirming the interpretation of the previous tracing

since the rest of the leads did not undergo important changes. The W-shaped complex in Leads I, V_L, and V_5 was strongly suggestive of a septal involvement (see preceding discussion). A few months later, the tracing (Fig. 14) underwent certain important changes. The W complex extended to V_6, and an M-shaped complex appeared in Lead V_1. The rest of the leads continued to be similar to

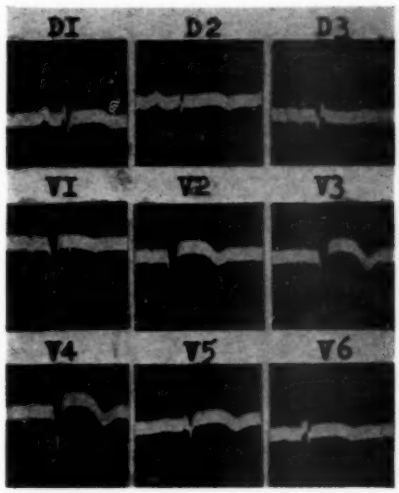

Fig. 11.—Extensive anterior infarct with anteroseptal necrosis.

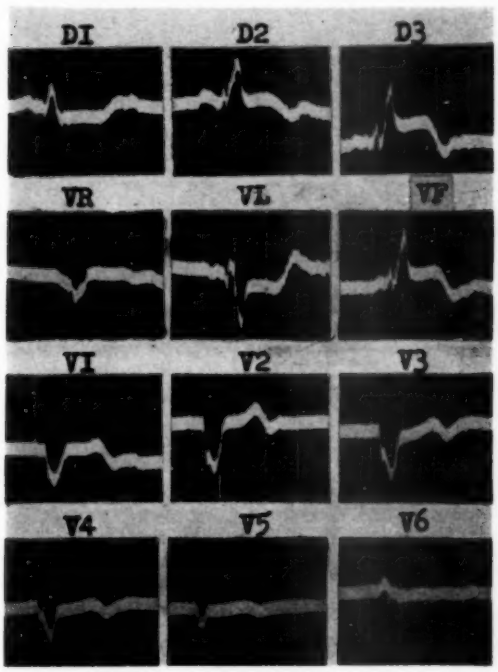

Fig. 12.—Recent posteroinferior infarct in the same patient as in Fig. 11.

those of previous tracings. At the present time, the tracing could be interpreted as that of incomplete right bundle branch block, but we believe that it is rather a left bundle branch block, belonging for this reason to the group we are now discussing.

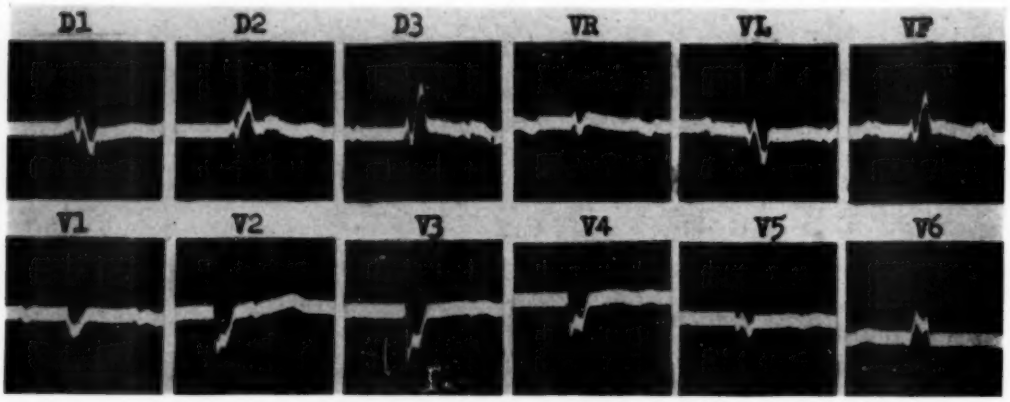

Fig. 13.—Tracing taken from the same patient as in Figs. 11 and 12 in which V_6 is strongly suggestive of left bundle branch block.

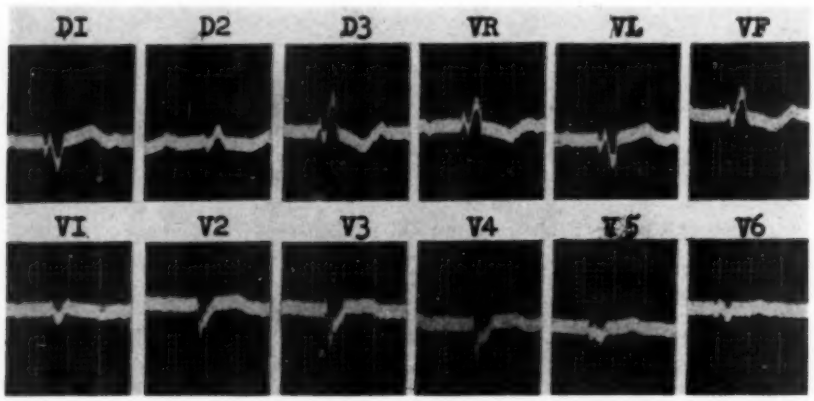

Fig. 14.—Tracing taken from the same patient as in Figs. 11, 12, and 13 in which there has appeared an M complex in V_1, which might erroneously suggest right bundle branch block.

COMPLETE OR INCOMPLETE LEFT BUNDLE BRANCH BLOCK, ASSOCIATED WITH MASSIVE INFARCTION OF THE INTERVENTRICULAR SEPTUM, WITH EXTENSIVE INVOLVEMENT OF THE FREE WALL OF THE LEFT VENTRICLE

Description of these cases was originally given by Wilson.[5] Peripheral leads, especially Leads I and V_L, suggest the defect in conduction. Precordial leads over the left chest are suggestive of an associated myocardial infarction. In V_5 and V_6 there are complexes of the QS type with slurrings and deep notches. Wilson suggested that this negativity is produced by forces originating in the

right ventricle and that the negativity of the right ventricular cavity coming from these forces is transmitted through the septal infarct to the cavity of the left ventricle and, through the infarction of the free wall of the left ventricle, transmitted also to the left precordial leads V_5 and V_6.

These infarctions, even though they damage the interventricular septum in a massive manner, do not involve some portions of the septum, especially those regions where the wave of activation is delayed when passing from the right to the left ventricle (Fig. 15). Otherwise, a bundle branch block could not be produced. These unaffected sites are proximal to the right septal surface and are formed mainly by the right ventricle. If some portions of the left ventricle in the septum are not involved, it is not possible to conceive of the presence of left bundle branch block in the interventricular septum.

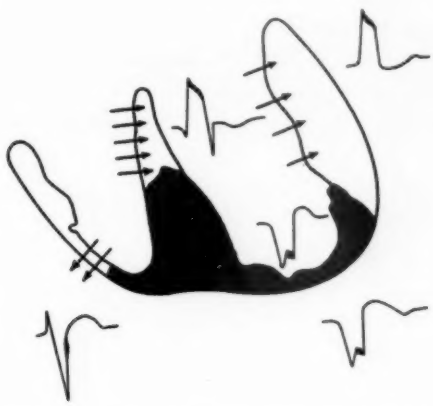

Fig. 15.—Schema to explain the morphology of the precordial leads in a case of left bundle branch block plus massive septal infarction.

Unaffected areas of the right ventricle show only negative complexes of the QS type due to the conduction disorder (Fig. 2). Actually, what happens is that the exploring electrode in V_5 and V_6 is oriented to the unaffected portions of the septum, especially those of the right ventricle (Fig. 15). The damaged tissue behaves only as a conductive tissue. At any rate, it is not possible to admit the destruction of the entire septum, for then we would have no basis to explain the left bundle branch block. Infarction may be massive and extensive, but some portions are respected.

DISCUSSION

Recently, First and co-workers[6] showed electrocardiograms which they considered suggestive of "peri-infarction block." These electrocardiographic patterns may often closely resemble those of bundle branch block or intraventricular blocks of other types. The authors suppose that "as contraction fibrosis occurs, the conducting strands would be subject to pressure atrophy and peri-infarction block would ultimately result. In cases where the block appears early, it would appear that strands of living muscle through the infarction do not exist or do not permit radial spread to the overlying normal wall. Recovery of function of the

fibers specified would, however, determine cessation of early temporary peri-infarction block, and failure of recovery would then determine early permanent peri-infarction block. Centripetal spread of activation parallel to the epicardial surface from the circumference of normal muscle overlying the infarct would be the natural result of failure of outward radial spread from the endocardial surface and since the former takes place at one tenth the speed normally encountered over the endocardial surface, the associated wave form is a function of the size of the blocked region relative to the position of the exploring electrode."

Many of the tracings described by First and associates are similar to ours, and in our opinion they are more suggestive of left bundle branch block than of peri-infarction block, since we have been able to obtain the same morphology not only within the ventricular cavity, but also over the septal surfaces in the presence of left bundle branch block.

Tracings taken on the septal surfaces of the left ventricle in cases of left bundle branch block and the bipolar transeptal tracings in cases of the same conduction disorder suggest that the origin of the slurring and the notching is essentially septal. Intracavity tracings also show the same slurrings belonging to the septum.

In several experiments we have injured wide areas of the left ventricular endocardium, and, working with direct unipolar leads, we have been unable to obtain changes in the morphology of the tracings, not even a slight delay in the intrinsic deflection.

Quite recently, Pruitt and co-workers[7] have produced a diffuse endocardial trauma (accomplished by instillation of potassium chloride, silver nitrate, phenol, or cocaine into the left ventricular cavity), and they did not produce increase in the width of the QRS complex. The phenomenon of arborization block was not reproduced by destruction or injury of these endocardial and subendocardial tissues.

It is true that the muscle fibers contained in the infarction are destined, in the majority, to suffer atrophy and death when a scar is formed since the collagenous fibers possess great retractile properties. The muscle fibers comprised in the scar area succumb not only to direct pressure due to connective retractile phenomena, but also to stenosis of the capillaries nourishing them. It is feasible, therefore, to admit focal block through the mechanism, as pointed out by First and associates, but up to the present time there are no direct proofs of delay at the site of the wall where the infarct is located. Because of this, we believe the diagnoses of focal block and of peri-infarction block should be proposed only when the possibility of bundle branch block is eliminated.

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AN ELECTROCARDIOGRAPHIC AND MORPHOLOGIC STUDY OF CHANGES FOLLOWING LIGATION OF THE LEFT CORONARY ARTERY IN HUMAN BEINGS: A REPORT OF TWO CASES

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BOSTON, MASS.

THROUGH animal experimentation and clinicopathologic correlation in human beings, many data have been accumulated in reference to the electrocardiogram and coronary artery occlusion. Traumatic cardiac surgery has given opportunities similar to the present one, and many such have been reported.[2-14, 29-31] It is believed, however, that the two cases reported here represent in vivo and post-mortem observations in human beings which have rarely been available.

Both of the following patients had rheumatic heart disease with severe disability from mitral stenosis, for the relief of which they underwent surgery. In each case, because of hemorrhage, it was necessary to place a suture in the region of the auriculoventricular groove in direct relation to the left main coronary artery or one of its branches.

CASE REPORTS

CASE 1.—H. F., a man, 47 years old, had chorea at the age of 17 years, but he was permitted to join the Navy at 19 years. He was first bothered by exertional dyspnea and hemoptysis at 43 years, but he did fairly well on digitalis and diuretics until the age of 45 years when he had a left pulmonary embolus with pleural effusion and severe pulmonary edema. Following this, the degree of incapacity became progressively greater, and, following complete studies including cardiac catheterization, it was decided that finger fracture valvuloplasty[32,33] of the mitral valve was indicated.

Physical examination revealed normal temperature, pulse, and respirations with a blood pressure of 100/60 mm. Hg. There was a moderate dorsal kyphosis and slight emaciation. Pulmonary examination suggested thickened pleura on the left, but no congestive signs were present. The heart was enlarged to the left with forceful impulse, accentuated pulmonary second sound, a loud systolic murmur, and a diastolic rumble with presystolic accentuation at the apex. Except for slight hepatomegaly and small psoriatic patches on the skin, examination was negative.

Laboratory Data.—Urine was negative. Hemoglobin was 12 Gm.; white blood cell count, 8,000; corrected sedimentation rate, 8 mm. per hour (Wintrobe); differential count, normal; Hinton, negative; blood urea nitrogen, 23 mg. per 100 c.c.; total protein, 8.3 Gm.; venous pressure, 13 cm. of water. The circulation times were 13 seconds (arm to lung with ether) and 20 seconds (arm to tongue with magnesium sulfate).

Course.—Preoperatively, the patient was comfortable on bed rest. Two bouts of auricular fibrillation were readily converted to sinus rhythm with quinidine. Cardiac catheterization was uncomplicated. At operation, under endotracheal gas-oxygen-ether, the left auricular appendage

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was isolated with some difficulty. Owing to the chest deformity and a marked posterior position of the left auricle, the operative exposure was far from satisfactory. Coincidentally with fracture of the mitral valve, a tear occurred in the auricle which extended to the auriculoventricular groove. Pressure transfusions were immediately started, and the edges of the tear were approximated with silk sutures. Six minutes and fifty-five seconds later the heart stopped beating. Cardiac massage was continued for seventy minutes without success.

A continuous electrocardiogram taken during the procedure revealed the following: From the initial incision until the placement of sutures in the left auricular appendage, the tracings remained quite unchanged except for a moderate tachycardia (Fig. 1, *A*). This obtained until two minutes and forty-five seconds prior to coronary ligation, coincidental with the first attempt at entrance into the auricle. Forty-five seconds prior to ligation, a second set of auricular sutures was placed, followed by a short period of ventricular tachycardia. At what was arbitrarily called time "zero," the finger fracture was performed with another burst of ventricular tachycardia,

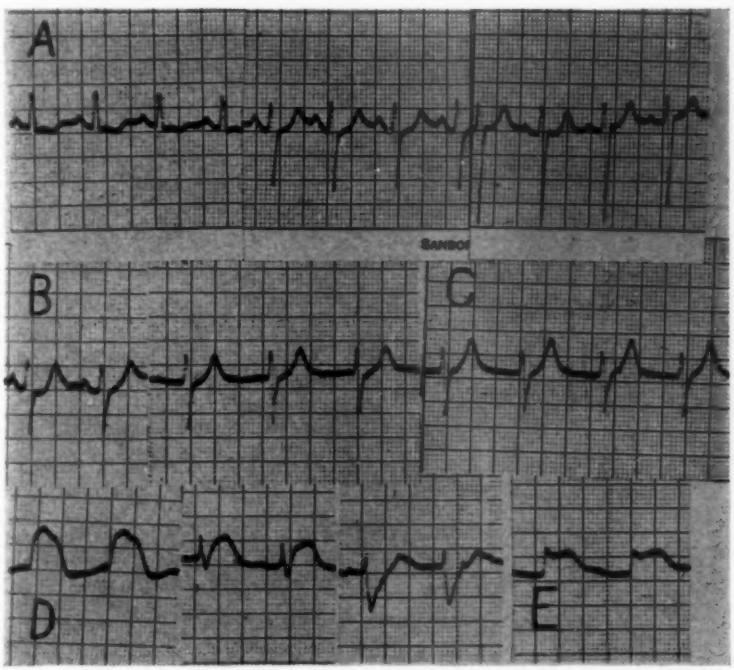

Fig. 1 (Case 1).—*A*, Leads I, II, and III; *B*, Lead II; *C*, Lead II; *D*, Leads I, II, and III; *E*, Lead II. Details discussed in text.

and the placement of clamps in the region of the left coronary artery was made in order to control bleeding from an auricular tear. At time thirty-three seconds, sinus rhythm was re-established with a Q-S of 0.10 to 0.12 second. At about three minutes and forty-five seconds after coronary ligation, a short period of frequent ectopic ventricular beats again appeared, and by four minutes and fifteen seconds, auricular activity had apparently ceased. At this stage (Fig. 1, *B*), T_2* was 5.5 mm. in height with slight, if any, S-T segment depression. At five minutes and ten seconds, T_2 became increased in height to 7.0 mm. (Fig. 1, *C*) and somewhat peaked. At five minutes and thirty-six seconds after coronary ligation (Fig. 2), the first sign of beginning elevation of the S-T segment in Lead II appeared, accompanied, as is seen, by brief bursts of ectopic ventricular discharge. The next full minute of tracing (Fig. 2) revealed progressive elevation of the S-T segment in Lead II with shortening of the S wave and diminished total voltage. No further

*Lead II was arbitrarily chosen for most of the tracing only because of the larger complexes more easily evaluated by the observer watching the writing arm.

widening of QRS took place during this period. Fig. 1, *D* shows Leads I, II, and III at six minutes and thirty-six seconds after ligation with reciprocal deviation of S-T segments in Leads I and III but without the appearance of Q waves as yet. Fig. 1, *E* shows the final, essentially monophasic Lead II just prior to the onset of ventricular fibrillation.

Autopsy restricted to the chest was performed eight hours post mortem. The heart weighed 500 grams. The entire epicardium revealed focal areas of hemorrhage due to the prolonged cardiac massage. The apex appeared somewhat softened over a radius of approximately 2 cm. The left auricular appendage had been amputated except for a cuff 0.5 cm. in width. The edges of the incision were coapted by black silk sutures. The myocardium was red brown with multiple areas of hemorrhage and softening throughout the left ventricle but without evidence of focal fibrosis. The cardiac chambers were dilated. The endocardium was not unusual except that of

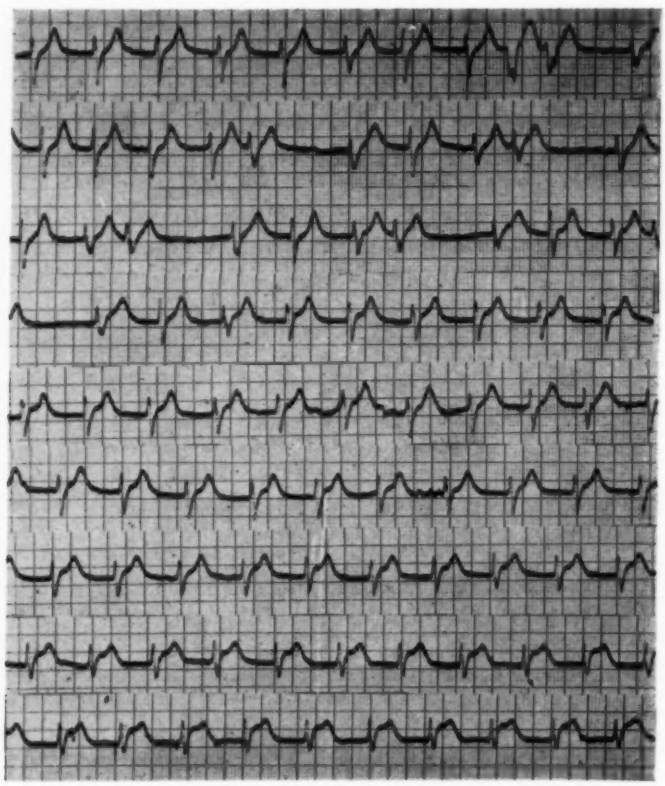

Fig. 2 (Case 1).—Continuous Lead II electrocardiogram for one minute beginning five minutes and thirty-six seconds after coronary artery ligation. Discussed in text.

the left auricle which contained a moderate-sized mass of ante-mortem mural thrombus. The valves were normal except the mitral which showed an extreme degree of stenosis, which would have permitted, in the preoperative state, the introduction of only the tip of the index finger due to the thickened, fused, and calcified ring. At the anterolateral commissure, there was a slitlike traumatic defect extending approximately 1 cm. through the stenosed mitral orifice and reaching the margin of the endocardium proper. With this surgically induced valvular defect, the mitral opening admitted the entire index finger and was quite mobile.

The ostia of the coronary arteries were patent, and the right coronary artery throughout its course was normal. However, numerous black silk sutures surrounded the left coronary artery at its major bifurcation (Fig. 3) and appeared to involve and occlude both the main arterial trunk and its branches, the circumflex and anterior descending arteries.

A roentgenogram of the heart following injection of the coronary arteries with opaque medium via the coronary ostia showed no filling of the left coronary tree although the major ramifications of the right coronary artery filled adequately. No other abnormalities of the heart were noted grossly.

Microscopically, the myocardium of the left ventricle presented subtle alterations consistent with very early infarction. Unequivocal evidence of recent infarction was noted in sections taken from the vicinity of the apex; these sections showed large, irregular cross striations of the myocardial fibers with clumping (Fig. 4), which is considered to be the earliest lesion demonstrable microscopically following myocardial infarction.[15] No other relevant gross or microscopic findings were noted.

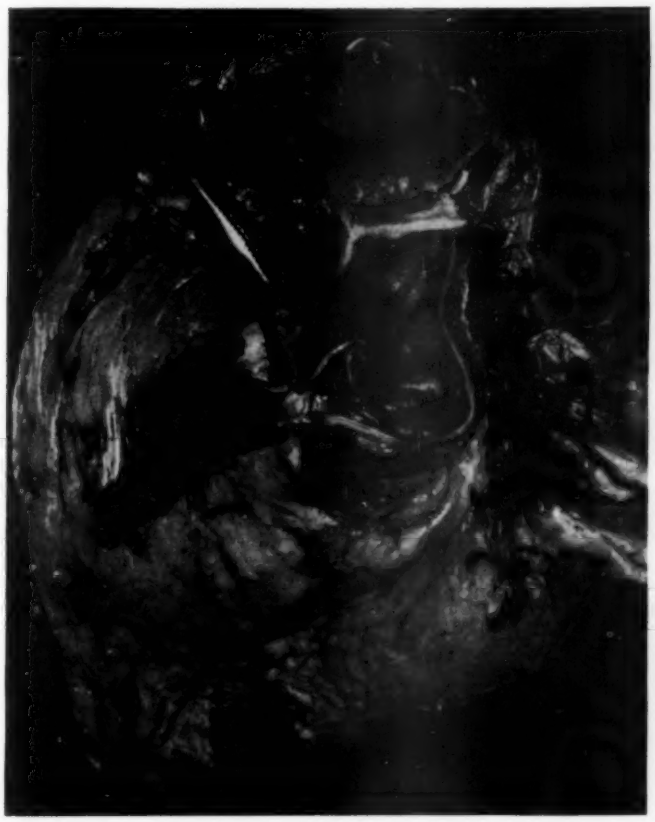

Fig. 3 (Case 1).—Anterior view of fixed, partially dissected heart showing mass of black silk sutures in vicinity of left auricle, many of which were found to have encircled and occluded the left coronary artery. The pulmonary conus is opened and retracted by a clamp.

Final anatomic diagnoses were: (1) rheumatic heart disease with calcific mitral stenosis, recent myocardial infarction in the left ventricle, secondary to occluding ligature of the left coronary artery, mural thrombus in the left auricle; (2) recent operation: cardiotomy, left auricular appendectomy, mitral valvuloplasty; (3) hemopericardium; (4) left obliterative fibrous pleuritis (etiology ? tuberculosis), bilateral basal pulmonary congestion and edema; (5) kyphoscoliosis; (6) psoriasis.

CASE 2.—H. J. McD., a woman 51 years old, had no history of rheumatic fever or chorea. In 1930, following severe pneumonia with endocarditis and pericarditis, she was first told that she had mitral stenosis. She was then digitalized, and for twenty years her activities as a nurse were

somewhat limited by exertional dyspnea, orthopnea, and ankle edema. She had had auricular fibrillation since 1934. She was forced to stop work in July, 1949, because of increasing symptoms and entered another hospital in February, 1950, because of severe dyspnea, paroxysmal nocturnal dyspnea, and ankle edema. Routine cardiac therapy including digitalis, diuretics, and salt-free diet was unsuccessful, and the patient was transferred to the Boston City Hospital for surgical therapy.

The relevant findings on *physical examination* were markedly dilated, pulsating neck veins, slight cyanosis, medium râles in the right lower lung field, and auricular fibrillation with cardiac enlargement to the right and left with loud, blowing systolic and soft, rumbling diastolic murmurs at the apex. The liver was markedly enlarged, smooth, and tender, and peripheral edema was present.

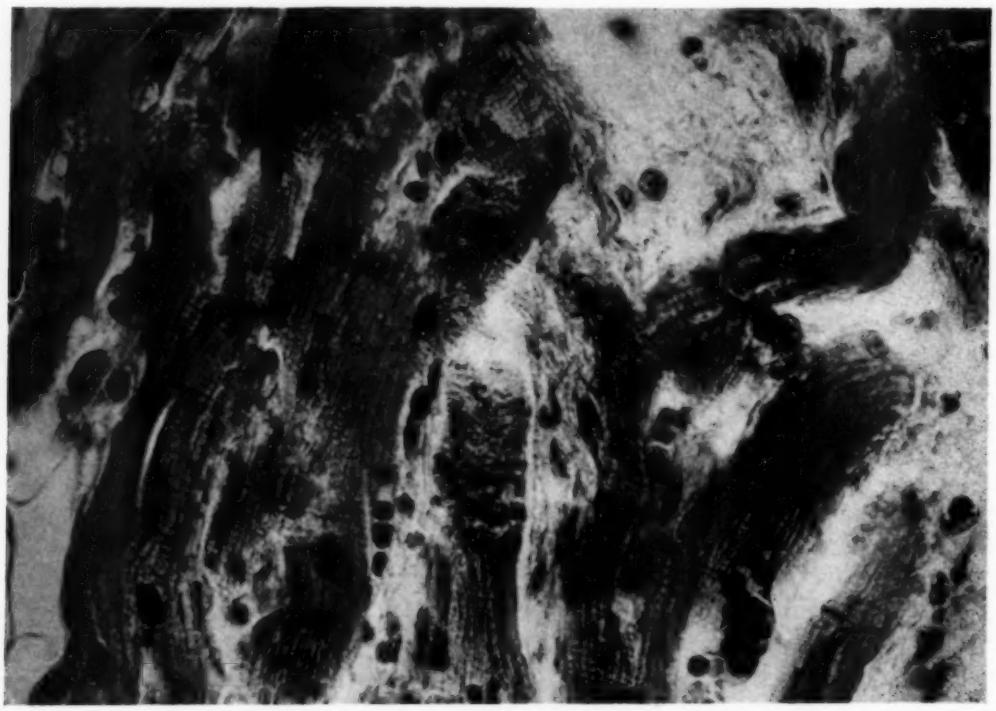

Fig. 4 (Case 1).—Photomicrograph of section from the apex of the left ventricle. Muscle fibers centrally located in the figure show two distinct foci of large, irregular cross striations. See text. (Hematoxylin and eosin, ×800.)

Laboratory Data.—The urine was normal; hemoglobin, 14 Gm.; white blood cell count, 8,400; total protein, 6.6. Gm.; Bromsulphalein retention, 6 per cent in forty-five minutes; prothrombin time, 74 per cent of normal; venous pressure, 24 cm. of saline; circulation time, 50 seconds (arm to tongue with magnesium sulfate). Cardiac catheterization studies were consistent with a severe grade of mitral stenosis.

Course.—The patient was in good condition when she went to the operating room for finger fracture mitral valvuloplasty. At operation, some difficulty was encountered in gaining entrance to the left auricular appendage because of a large, fixed thrombus. Following fracture of the valve, a tear occurred in the left auricle, extending to the auriculoventricular groove and requiring a clamp and sutures to be placed in the region of the bifurcation of the left coronary artery. Although blood pressure was, for a few minutes, unobtainable, bleeding was controlled, and the patient was returned to the ward. Blood pressure returned to levels only slightly below pre-

operative values. The patient never became lucid enough to describe carefully any chest pain, although she did complain of precordial "squeezing."

Twelve hours postoperatively she developed a left hemiplegia, the temperature rose rapidly, and she died twenty-four hours later with peripheral vascular collapse. Death appeared to be due to massive cerebral embolism.

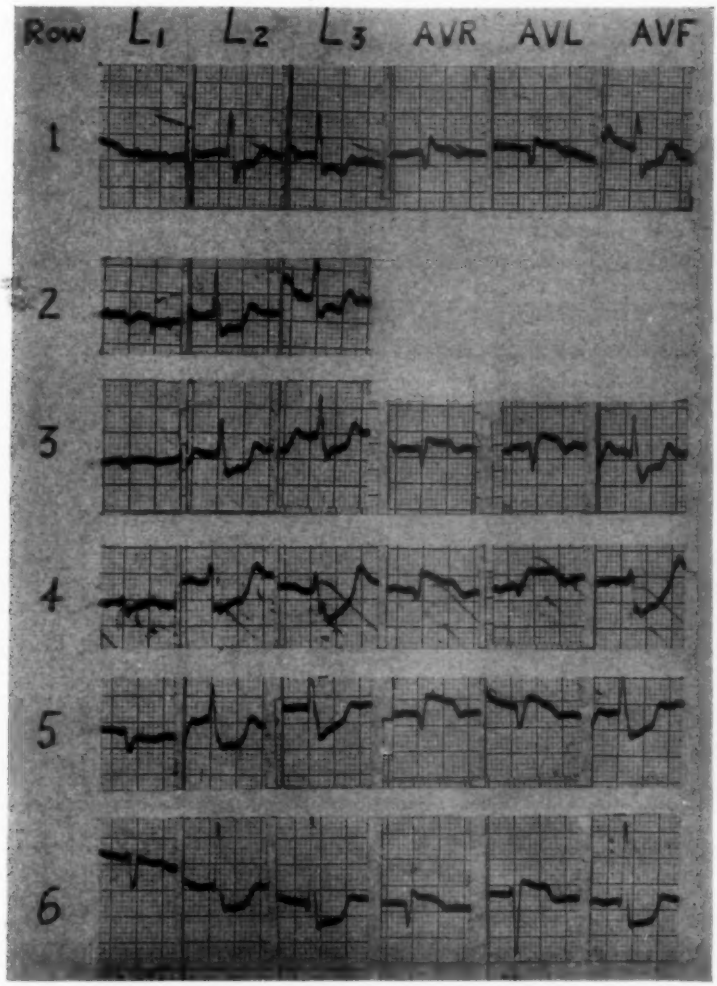

Fig. 5 (Case 2).—Top row: Leads I, II, III, aV_R, aV_L, and aV_F. Second row: Leads I, II, and III. Third to sixth rows: Leads I, II, III, aV_R, aV_L, and aV_F. Details discussed in text.

Continuous electrocardiograms were taken during the operative procedure and were repeated frequently after operation. Fig. 5, top row, shows Leads I, II, III, aV_R, aV_L, and aV_F as they appeared both preoperatively and just prior to opening the left auricular appendage. These showed S-T segment deviations consistent with digitalis effect and probable right ventricular hypertrophy. Fig. 5, row 2, shows Leads I, II, and III taken five minutes after the initial placement of the clamp in the region of the left coronary artery. Here S-T segments in Leads II and III had begun to show slight depression with a suggestion of elevation in those of Lead I. At seven minutes after coronary occlusion (Fig. 5, row 3), S-T segments in Leads II, III and aV_F showed more marked depression with beginning further elevation of S-T in Leads aV_R and aV_L.

At ten minutes (Fig. 5, row 4), the previous changes had become marked and had reached their maximum deviation. Tracings taken at eighteen minutes (Fig. 5, row 5) and again at thirty-one minutes (Fig. 5, row 6) following coronary ligation showed beginning regression of the S-T segment changes. It is of interest that no significant Q waves appeared during the entire time except, perhaps, in Lead aV_L at eighteen minutes. Tracings not shown, taken four and twenty-eight hours following the injury and ligation of the left coronary artery and consisting of the six leads taken above (chest leads were omitted because of extensive bandaging), showed further reversion toward the preoperative picture, with no signs consistent with the evolution of a myocardial infarction.

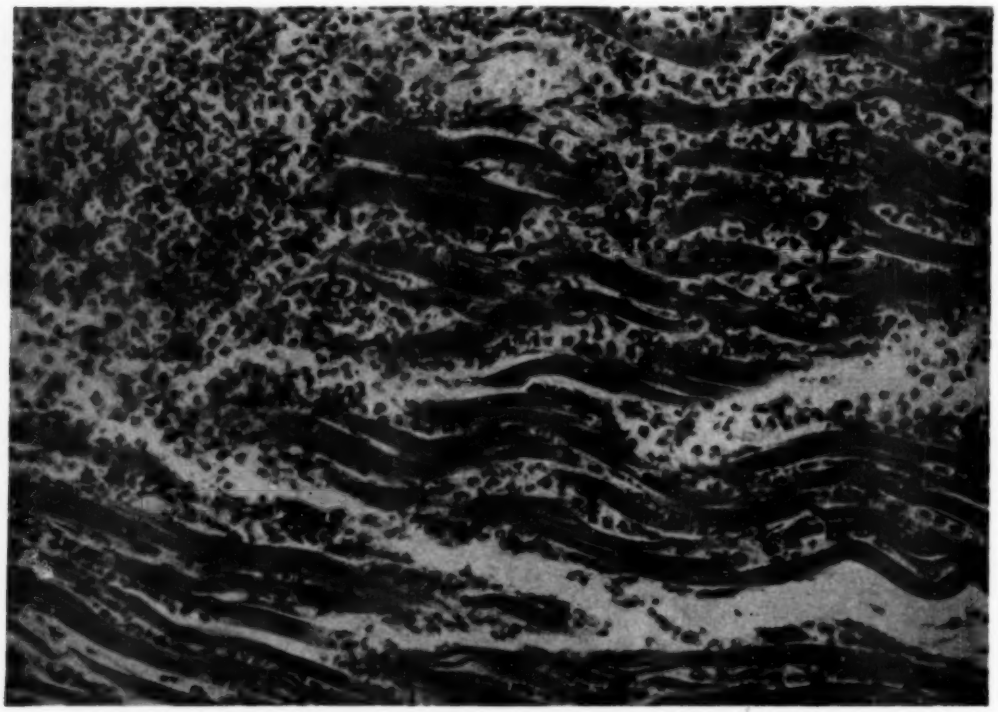

Fig. 6 (Case 2).—Photomicrograph from section of the anterior aspect of the left ventricle. Discussed in text. (Phloxine-eosin azure-methylene blue, ×400.)

Autopsy was performed fifteen hours post mortem. The heart in situ presented an enormously dilated right auricular appendage. It weighed 500 grams. The left auricular appendage had been amputated in toto, and overlying the suture line was a mass of Oxycel, used during the operation for hemostasis. The myocardium was relatively firm and red brown except throughout the left ventricle and interventricular septum, where it appeared mottled purplish red and yellow. The right ventricle was increased in thickness, approaching that of the left. No mural thrombi were present. Only the mitral valve was abnormal. It was markedly stenosed and permitted the introduction of only the tip of the index finger when the ring was held in a position simulating the preoperative state. However, there were two recent traumatic defects, the larger in the vicinity of the anterolateral commissure and measuring 0.5 cm. The smaller was directly opposite and measured 0.3 cm. With the surgical defects considered, the valve admitted the entire index finger. The mitral orifice, apart from the sites of operative fracture, was extremely calcified and firm with marked thickening, rolling of the margins, and nodularity. The chordae tendineae were shortened, fused, thickened, and whitish. The ostia of the coronary arteries were patent, and the right coronary artery was free of occlusion or significant sclerosis throughout its major

distribution. The left coronary artery was seen to plunge into a dense mass of heavy black silk sutures approximately 1.5 cm. from its ostium. The ligatures appeared to be drawn tightly about either the main arterial trunk or the origin of the anterior descending branch. It was difficult, because of adjacent reaction, to determine if the main trunk was effectively occluded. The lumina of the circumflex and anterior descending branches of the left coronary artery were, however, free of ante-mortem clot.

Microscopically, the oldest myocardial lesions were present in sections taken from the anterior wall of the left ventricle and consisted of a marked polymorphonuclear leucocytic infiltration involving the interstitial tissue and tending to spread between necrotic muscle fibers (Fig. 6). Such changes were considered consistent with the clinical age of the myocardial infarction at the time of death. In addition, other sections of the left ventricle presented foci which showed earlier changes, such as increased eosinophilia, large irregular cross striations, blurring of longitudinal striations, and vacuolation suggesting fat. These alterations perhaps represent more recent infarction following secondary thrombosis of smaller arterioles. Occasional foci of myocardial fibrosis were seen microscopically as well as evidence of coronary atherosclerosis and hemorrhage into epicardial fat; the latter were related to surgical trauma. Sections of the right ventricle showed no changes suggestive of infarction.

Final anatomic diagnoses were: (1) cerebral embolism; (2) calcific rheumatic mitral valvulitis, old, with stenosis; (3) recent operation (thirty-six hours): thoracotomy, left auricular appendectomy, mitral valvuloplasty; recent myocardial infarction of the anterior wall of the left ventricle secondary to ligation of the anterior descending branch of the left coronary artery; postoperative fibrinous pericarditis; (4) recent infarcts (three), small, lower pole of right kidney.

DISCUSSION

The electrocardiographic, clinical, and pathological events following operative ligation of coronary arteries without prior ventricular trauma and with continuous electrocardiographic monitoring have not to our knowledge previously been reported. There were in the cases reported here certain acute complicating factors in addition to the underlying chronic heart disease. Recently, Master and co-workers[16] reviewed the subject of coronary insufficiency and electrocardiographic abnormalities associated with acute hemorrhage and shock. Significant changes in their series consisted of inverted T waves and depressed S-T segments, chiefly over the left ventricle, suggestive of subendocardial ischemia. Hemorrhage and shock occurred in both patients reported here. However, the location of the ligatures, the post-mortem findings, and the type of electrocardiographic changes are evidence that the occlusion was the important factor. For the same reasons and because of the care of the operator, actual handling of the heart during operation may be discounted, especially since firm massage took place only in Case 1 and only after the onset of ventricular fibrillation.

In human beings, time relationships in the evolution of the electrocardiographic pattern of myocardial infarction in the past had to be inferred from clinical results and animal experiments. Bayley and co-workers,[17-19,23] Harris and Hussey,[20] Barnes and Mann,[21] Blumgart and co-workers,[22,24] and others have demonstrated a current of injury manifested in S-T segment deviations in dogs as soon as forty seconds after coronary artery occlusion. Blumgart and co-workers[24] and Mallory and associates[27] have pointed out that dog experiments in several ways do not reproduce exactly the course of events in human beings with already diseased hearts, and therefore definite conclusions cannot be drawn from such evidence.

Both clinically[1] and experimentally, ectopic rhythms and ventricular irritability have been demonstrated under the same circumstances, often terminating, as in Case 1, in ventricular fibrillation. Of interest also are the recent reports of Hellerstein and Liebow,[25] demonstrating the frequent early increase in the height of the T wave in leads facing the injured myocardium. Assuming, as Prinzmetal and co-workers showed,[26] that coronary occlusion may first result in the greatest ischemia to the subendocardial muscle, the finding of Bayley and La Due[17] that the ischemic manifestations on the T waves precede the injury effects shown in the S-T segments is quite consistent with this early T-wave peaking. That phenomenon was clearly demonstrated in Case 1 with an increase in T-wave height which occurred five minutes after ligation, beginning elevation of $S\text{-}T_2$ five minutes and thirty-six seconds after ligation, and a completely monophasic current of injury in Lead II at six minutes and fifty seconds, followed within five seconds by ventricular fibrillation. The total picture of Leads I, II, and III just before the latter fatal event was entirely consistent with massive anterior myocardial infarction. Case 2 showed the earliest S-T segment deviation also at five minutes after coronary occlusion with maximum deviation, almost monophasic in character, ten minutes after ligation. It is therefore evident, at least in a previously diseased heart in the anesthetized human being, that electrocardiographic evidence of myocardial injury can appear five minutes after occlusion of the blood supply to the myocardium with rapid progression of the electrocardiographic pattern and with the almost immediate appearance of marked ventricular irritability.

In 1939, Mallory and co-workers[27] stated that it is difficult to find histological evidence of infarcted myocardium until five or six hours after coronary occlusion, but, more recently, Mallory[15] has altered his opinion and states that probably the earliest histological evidence of myocardial infarction is the demonstration of large irregular contraction bands in the affected muscle fibers. The microscopic sections from Case 1 (Fig. 4) in which death occurred almost immediately after the left coronary artery was ligated support this opinion, since this occurred in a focal fashion throughout the left ventricular myocardium. Distended venules and capillaries were also noted, but it is felt that these findings are of somewhat dubious significance in relation to myocardial infarction.

In Case 2 in which the patient died thirty-six hours after operation, the finding of a marked, but not maximal, polymorphonuclear leucocytic infiltration interstitially and between muscle fibers was consistent with the clinical duration of the infarction. Other histological evidence of necrotic muscle was also noted in the form of increased acidophilia, blurring of longitudinal striations, eosinophilic granules, and extravasation of blood; some appeared to indicate more recent infarction in focal areas, probably related to propagation of the thrombus with infarction in previously uninvolved areas.

It is not clear why Case 2 showed rapid reversion toward normal in the electrocardiogram despite the eventual proof of myocardial infarction of about thirty-six hours' duration. Perhaps an initially extensive area, made apparently larger by the presence of profound shock, became reduced in size following reestablishment of a more efficient blood flow. Perhaps the true zone of infarcted

muscle did not extend to either the epicardial or endocardial surfaces of the heart. Probably, if it had been possible to get chest leads, these questions could be answered. The important implication is, of course, as Levy and Hyman[28] recently stressed, that the electrocardiogram is not infallible, especially when "insufficient" exploring leads are taken.

SUMMARY

Two patients with rheumatic heart disease with mitral stenosis are reported, both of whom were operated upon for the purpose of performing a mitral valvuloplasty. Both patients were closely followed electrocardiographically. During the operation, surgical emergency therapy resulted in the ligation of the left coronary artery. The pattern of acute myocardial infarction appeared in both cases. It proceeded to rapid death in one case and regressed in the other. At post-mortem examination, both showed the suspected ligation, and the histological picture of an infarcted myocardium of the appropriate age was found. The cases are discussed with respect to (1) possible influence of shock and hemorrhage, (2) electrocardiographic pattern and time relationships, (3) the pathology involved, and (4) possible explanations of the reversion of the electrocardiographic pattern in the second case.

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EFFECT OF THE CHANGE FROM SUPINE TO SITTING POSITION ON THE CHEST LEADS

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IT HAS long been known that the position of the heart has an effect on the electrocardiogram,[1] but, despite the large literature (recently reviewed by Brofman and associates[2]) few studies with a quantitative analysis of positional changes have been reported. Specifically, no adequate analysis of positional differences in the chest leads in the sitting position is available. It is the purpose of this study to provide such information.

For the diagnostic use of postural electrocardiographic changes, as repeatedly suggested,[2-5] the comparison between supine and sitting position appears to be more practical than the comparison between supine and standing position, since the sitting position can be investigated in most bedridden patients. Another reason for this study is the introduction of back leads[6,7] for electrocardiographic diagnosis. Back leads, as a rule, are taken in the sitting position while the precordial leads are taken in the supine position. In case of large positional changes, a break in the trend of electrocardiographic patterns should be expected, which might be of consequence for the interpretation.

METHOD AND SUBJECTS

After a rest of at least ten minutes, the standard limb leads, unipolar limb leads, V_{1-6}, V_{5R}, and V_{6R} were taken in the supine position, and V_2, V_6, and V_{6R} were repeated in the sitting position. The QRS and T deflections were measured, and the initial values (supine position), as well as the changes from supine to sitting position, were evaluated by means of accepted statistical methods.

The subjects were twenty-three normal men who were screened as to the absence of clinical disease in a careful clinical examination. They were selected from a larger group to get approximately an even distribution of electrical heart positions, determined by means of the unipolar limb leads. The heart position was horizontal (H) or semihorizontal (SH) in seven, intermediate (I) in eight, and vertical (V) or semivertical (SV) in eight subjects.

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RESULTS

The first two rows of Table I show the means and standard deviations of the main QRS deflections and of the T wave in the supine position. The Q wave and S wave in V_6 (and the r or r′ wave in V_{6R}) were not evaluated because the error of measurement[8] is too large for the small amplitudes involved here. The main QRS deflection in V_{6R} was a Q wave, an S wave, or a QS wave, but was negative in any case. No differentiation of these was made in this analysis. The standard deviations indicate the interindividual variability, which was found to be comparable to the interindividual standard deviation of the QRS and T deflections in CF_2 and CF_4 in twelve normal young men.[5]

TABLE I. MEANS (M) AND STANDARD DEVIATIONS (S.D.) OF MAIN QRS AND T WAVES OF 23 NORMAL MEN IN SUPINE POSITION (ROWS 1, 2), MEAN DIFFERENCES (M. △) BETWEEN SUPINE AND SITTING POSITIONS WITH S.D. (ROWS 3, 4), AND RANGE LIMITS OF THE POSTURAL CHANGE FOR 98 PER CENT OF NORMAL POPULATION (ROWS 5, 6). (THE SIGN + INDICATES AN INCREASE, − A DECREASE, OF THE AMPLITUDE IN THE SITTING POSITION.)

		V_2			V_6		V_{6R}	
		R	S	T	R	T	QS	T
Supine	M.	5.12	12.88	5.60	11.95	3.16	2.51	−0.87
	S. D.	2.89	1.47	1.77	3.14	1.10	1.21	0.35
Sitting	M. △	−0.47	−0.42	−0.19	−0.03	−0.27	+0.03	+0.03
	S. D.	0.51	1.39	0.72	1.44	0.52	0.52	0.13
Upper	Limit △ +	+0.72	+2.83	+1.49	+3.33	+0.94	+1.24	+0.33
Lower		−2.66	−3.67	−1.87	−3.39	−1.48	−1.18	−0.27

The second and third rows show the mean differences between the supine and the sitting positions and their standard deviations. A plus (+) sign means an increase, and a minus (−) sign means a decrease of the amplitude, independent of its direction. The mean change was small in all leads and deflections and was statistically significant from zero only for the R wave in V_2 ($t = 4.47$; $P = 0.001$). In no case was there any change of the electrocardiographic pattern. The small mean change does not necessarily exclude large and scattered individual changes. However, the standard deviations of the mean changes were relatively small compared to the mean amplitudes (row 1), although they were large compared to the small positional changes. From the standard deviations, the expected range limits were calculated for 98 per cent of normal population (rows 5 and 6). Since the standard deviation includes the error of measurement, which is not negligible[8] in view of the small differences between the supine and sitting positions, the calculated range limits are an exaggeration of the true postural changes.

Table II shows the mean postural changes in the subgroups of seven men with horizontal or semihorizontal hearts and the eight men with vertical or semivert ical hearts. The differences between these partial positional groups were

statistically not significant. As an example, Fig. 1 shows the electrocardiograms of six men in supine (*A*) and sitting position (*B*). In subjects No. 470 (SH), 250 (I), and 276 (I), R_{V2} is somewhat smaller, and in No. 470, S_{V6} is somewhat larger, in the sitting position, but the changes are slight and practically absent in subjects No. 395 (V), 408 (SH), and 1008 (I).

TABLE II. MEAN CHANGE OF QRS AND T WAVES FROM SUPINE TO SITTING POSITION IN 7 MEN WITH HORIZONTAL (H) OR SEMIHORIZONTAL (SH) HEART POSITION AND IN 8 MEN WITH VERTICAL (V) OR SEMIVERTICAL (SV) HEART POSITION

	V_2						V_6			
	R		S		T		R		T	
	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.	MEAN	S. D.
H, SH	−0.41	0.71	−0.84	1.14	−0.29	0.65	−0.14	1.13	−0.29	0.32
V, SV	−0.54	0.40	−0.50	1.91	−0.19	0.93	+0.35	0.65	−0.25	0.60

DISCUSSION

The absence or small magnitude of effects of the postural change from the supine to the sitting position seems to be at variance with the general impression from the electrocardiographic literature. However, most of the published data are concerned with the response in the limb leads to the standing position. The following reasons can be given for the apparent discrepancy: (1) The electrocardiographic response to the standing position is due not only to mechanical positional effects.[3,5,9-12] The mechanism of the functional electrocardiographic postural changes is not yet clearly understood, but they probably reflect changes in blood distribution which are much less pronounced in the sitting position. (2) A tendency toward a vertical heart position in the upright body position is related to the downward displacement of the abdominal organs in the standing position; this displacement is small in the sitting position. (3) The chest leads are closer to the axis of rotation of the heart than the standard or unipolar limb leads.

Actually, our results agree fairly well with observations of other authors, who emphasized, however, the presence of postural changes in the standard leads rather than the absence of such changes in the chest leads. In the great majority of Sigler's[12] patients Lead IV did not change in the sitting position. Jones and co-workers[13] stated that "the precordial potentials remained of the same general form," which probably refers to the response to sitting as well as to lateral positions. Even in patients with left bundle branch block or left ventricular preponderance, who showed striking postural electrocardiographic changes in the limb leads, the precordial potentials were substantially unchanged.

There is also not necessarily a discrepancy between our results and the successful use of postural electrocardiographic changes in sitting or lateral positions for the diagnosis of myocardial infarct by Brofman and associates.[2] In

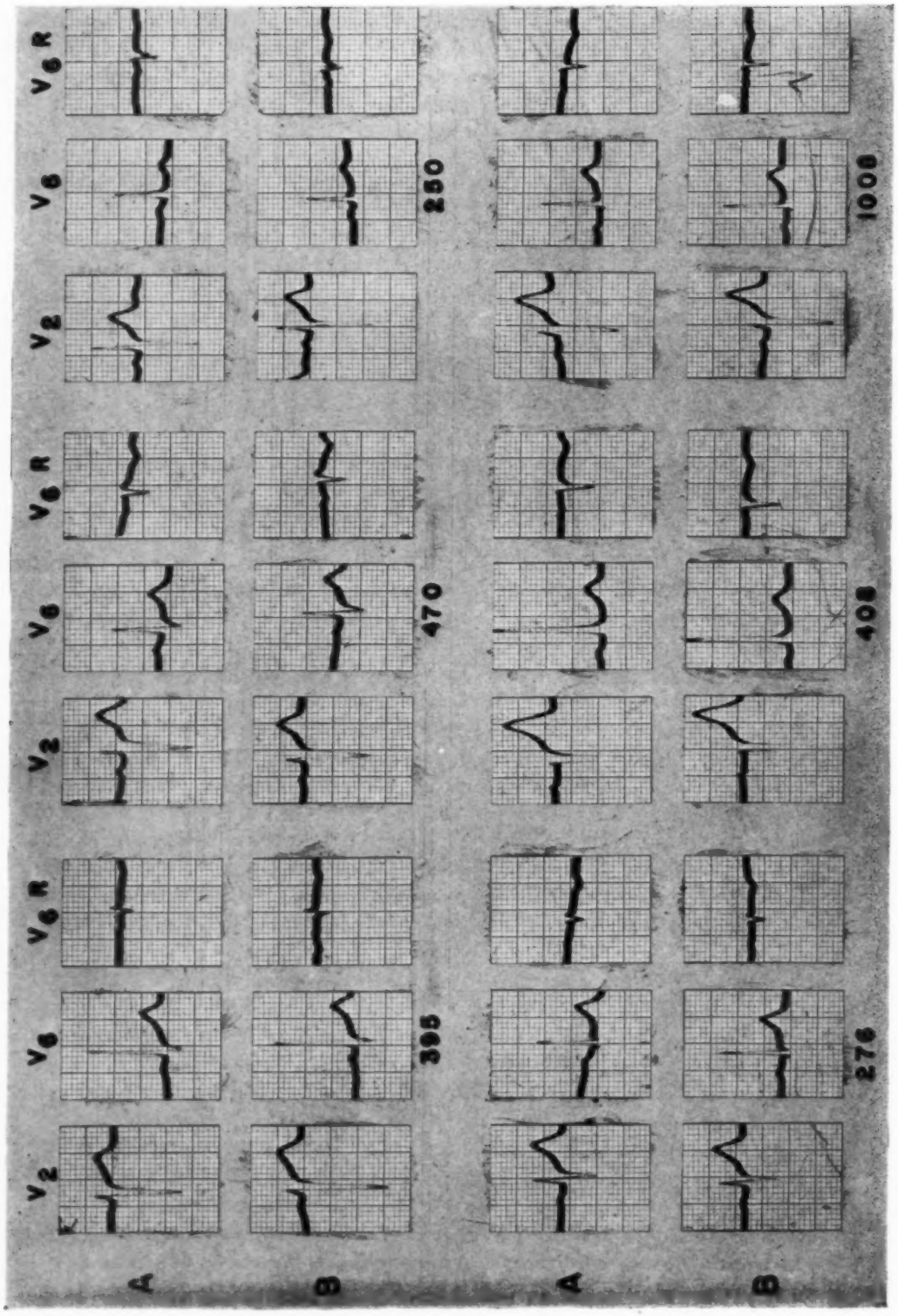

Fig. 1.—Typical electrocardiographic changes from the supine (*A*) to the sitting position (*B*) in three precordial leads of six normal men.

their Figs. 1, 2, and 5 which refer to a comparison between the supine and the sitting positions, the changes in V_2, V_4, and V_6 were minor and of no diagnostic value. In their Table II, the incidence of clockwise or counterclockwise rotation of the heart on its long axis was tabulated; the great majority of patients did not show any change in the sitting position. However, the absence of normal controls and of quantitative evaluation in their study should be noted. It is, of course, quite possible that in some patients the changes in sitting position might be larger than those of normal subjects. This could be due to a different configuration or location of the vector or to functional postural effects such as occur in normal subjects in standing position. The small magnitude of the electrocardiographic changes in the chest leads in the sitting position has no direct bearing on the usefulness of this procedure for differentiation between normal and abnormal electrocardiograms. The response may be considered as abnormal when definitely outside the normal range limits as given in Table I.

Since the changes in V_2, V_6, and V_{6R} are small or absent, it can be inferred that they are small also in the other precordial leads. It follows from our finding that no break in the trend of pattern distribution need be considered if back leads, taken in the sitting position, are compared with precordial leads taken in the supine position.

SUMMARY

1. The electrocardiographic changes from the supine to the sitting position were analyzed in V_2, V_6, and V_{6R} for twenty-three healthy men.

2. The mean differences of the QRS and T amplitudes were small and were not significantly different from zero except for the mean decrease of the R wave (−0.47 mm.).

3. There was no significant difference in the response in men with horizontal or semihorizontal hearts when compared with men with vertical or semivertical hearts.

4. The range limits of the expected change were calculated for 98 per cent of the men in a "normal" population.

5. The apparent discrepancy of these results and the electrocardiographic responses to the standing position in the standard leads is discussed.

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ANGIOCARDIOGRAPHIC CONFIRMATION OF PERICARDIAL EFFUSION

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DURING the past year we have had the opportunity to make angiocardiograms of eleven patients to confirm or rule out the presence of pericardial effusion. Exposures were taken at the rate of one per second at 150 Ma. and 115 kv. on 70 mm., green sensitive film, utilizing a photofluorographic technique with a Fairchild 70 mm. camera with an Eastman Fluoro Ektar F: 1.5 lens, Patterson type B-2 screen, and a Super-Dynamax tube. Eight cases will be briefly summarized.

CASE REPORTS

CASE 1.—A. M., a Negro female infant, 18 months old, was referred to Charity Hospital on Aug. 18, 1950, following two weeks of therapy for bronchopneumonia at another institution. Physical examination revealed a temperature of 101° F., blood pressure 90/84-72 mm. Hg, paradoxical pulse, distended neck veins, marked cardiac enlargement, distant heart sounds, and hepatomegaly. X-ray examination revealed marked cardiac enlargement to the right and left. An electrocardiogram showed low complexes throughout. An angiocardiogram (Fig. 1) revealed the presence of a large opacity outside the limits of the cardiac chambers.

Repeated pericardiocenteses and a pericardiostomy were performed with removal of greenish purulent fluid on all occasions, confirming the diagnosis of purulent pericarditis. Smear and stain of the pericardial fluid revealed gram-positive diplococci; however, all cultures were negative.

The patient received penicillin and aureomycin. Streptomycin and streptodornase were placed in the pericardial sac. Following therapy for purulent pericarditis, the patient developed congestive heart failure which responded to digitalis, salt limitation, and mercurial diuretics.

CASE 2.—A. S., a Negro woman, 34 years old, was admitted to the hospital on Nov. 16, 1950. She had had an episode of severe precordial pain lasting one hour three months prior to admission. She was asymptomatic on admission. Physical examination revealed no pertinent findings except for a blood pressure of 115/85 mm. Hg and the presence of marked cardiac enlargement to the right and left. X-ray examinations confirmed the presence of marked cardiac enlargement. An angiocardiogram (Fig. 2) demonstrated the presence of opacity outside the limits of the cardiac chambers. Five hundred cubic centimeters of straw-colored fluid were obtained by pericardiocentesis. All laboratory tests for acid-fast bacilli were negative.

The final diagnosis was probable tuberculous pericarditis.

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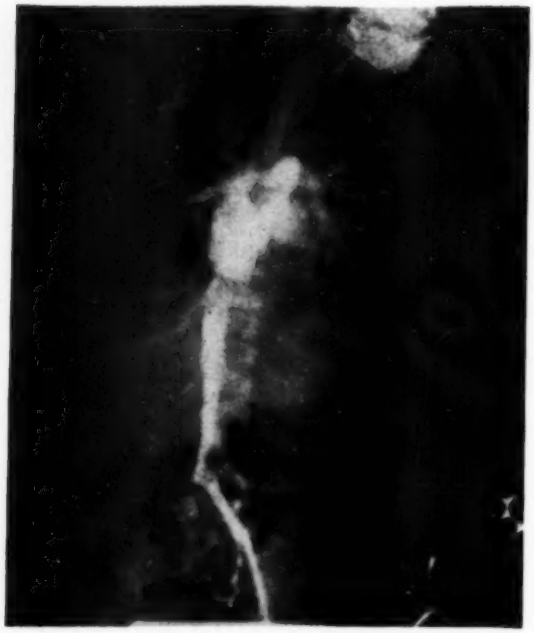

Fig. 1.—Film two and one-half seconds after injection of contrast medium, outlining the right cardiac chambers and pulmonary arteries and demonstrating a large opacity outside the limits of the right ventricular chamber and pulmonary artery.

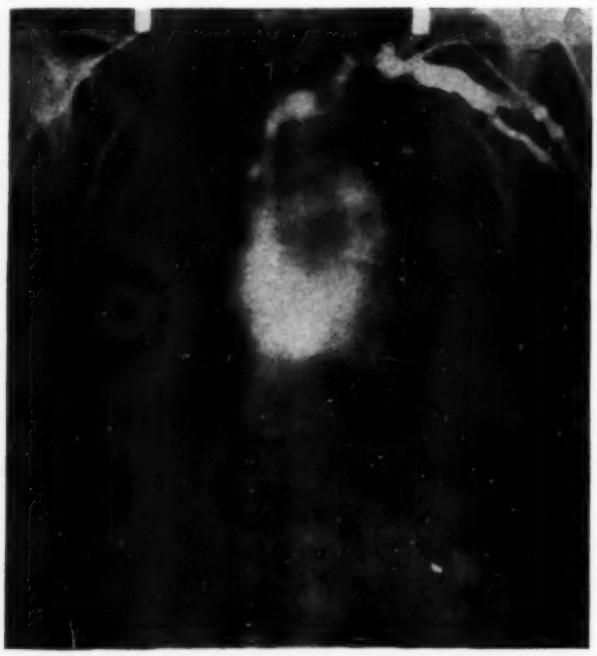

Fig. 2.—Film taken four seconds after injection of contrast medium, outlining right ventricle and pulmonary arteries and demonstrating a large opacity outside the limits of the right ventricle and pulmonary artery.

CASE 3.—B. B., a white girl, 7 years old, was admitted to Charity Hospital on March 12, 1950, with a history of being chronically ill and running a low-grade fever for three months. Physical examination revealed generalized lymphadenopathy, clubbed fingers, evidences of polyserositis, and anemia. The cardiac shadow was markedly enlarged to the right and left. Extensive laboratory investigations were performed without revealing any definite etiology for the polyserositis.

An angiocardiogram revealed the presence of an opacity outside the limits of the cardiac chambers (Fig. 3). Five hundred cubic centimeters of serosanguineous fluid were obtained by pericardial tap.

The final diagnosis was disseminated lupus erythematosus.

CASE 4.—K. G., a Negro woman, 46 years old, was readmitted to Charity Hospital on Jan. 25, 1950, having been treated in the outpatient clinic at intervals since September, 1945, for hypertensive cardiovascular disease with left- and right-sided congestive heart failure. During the four months prior to Jan. 25, 1950, she had become progressively worse, requiring two abdominal paracenteses and failing to respond to therapy.

Physical examination revealed a blood pressure of 176/112 mm. Hg, marked dyspnea, paradoxical pulse, marked cardiac enlargement with a moderately forceful apical impulse in the sixth intercostal space in the anterior axillary line, accentuated aortic second sound, hepatomegaly, ascites, and edema of the lower extremities. Roentgen examinations revealed marked cardiac enlargement to the right and left with diminished amplitude of pulsation. An electrocardiogram was compatible with left ventricular hypertrophy. An angiocardiogram (Fig. 4) confirmed the presence of opacity outside the limits of the cardiac chambers. Repeated pericardiocenteses were performed during the next month with a total of 4,930 c.c. of serosanguineous fluid being removed. Air injected into the pericardial sac following pericardiocentesis demonstrated the presence of hydropneumopericardium and ruled out the possibility of the fluid being outside of the pericardium.

CASE 5.—D. B., a Negro boy, 3 years old, was admitted to Charity Hospital on Feb. 13, 1951, with a history of an upper respiratory infection one week prior to admission followed by generalized joint pains, temperature elevation to 105° F., and bilateral pneumonitis. A diagnosis of rheumatic fever was made, and during the patient's stay in the hospital he developed signs suggestive of a pericardial effusion. An angiocardiogram (Fig. 5) revealed an opacity outside the limits of the cardiac chambers. Pericardiocentesis was performed, and 60 c.c. of serous fluid were removed. Biopsy of a subcutaneous nodule was compatible with rheumatic fever, Aschoff bodies being seen in the biopsy specimen.

CASE 6.—V. C., a white girl, 7 years old, was admitted to Charity Hospital on Jan. 31, 1951, with a two-week history of dyspnea, fever, and nonproductive cough.

Pertinent points on physical examination were a temperature of 102.4° F., a blood pressure of 100/80 mm. Hg, lungs clear to auscultation, marked cardiac enlargement to the left, apex impulse of moderate intensity in the fifth intercostal space in the anterior axillary line, heart sounds of normal intensity, a loud systolic murmur over the aortic area which was transmitted into the neck, a pericardial friction rub near the sternum in the fourth left intercostal space, and hepatomegaly. Venous pressure was 160 mm. of water. The sedimentation rate, corrected, was 42 mm. in one hour. The only electrocardiographic abnormality was low amplitude of $T_{1,2,3}$. Roentgen examinations revealed moderate cardiac enlargement to the right and left with slight diminution in the amplitude of pulsation. An angiocardiogram (Fig. 6) confirmed the presence of an opacity outside the limits of the cardiac chambers. The patient was placed on salicylate therapy with subsequent remission of symptoms and signs and gradual regression of heart size. The aortic murmur remained.

The final diagnosis was rheumatic carditis versus acute benign pericarditis.

CASE 7.—L. B., a Negro girl, 10 years old, developed symptoms and signs of acute rheumatic fever with carditis and was transferred to Charity Hospital on Feb. 3, 1951, from an institution where she had been receiving therapy for congenital syphilis. There was a past history of chorea in 1948. Upon admission to Charity Hospital, pertinent findings were: blood pressure 110/70 mm. Hg, temperature 99.4° F., pericardial friction rub, heart sounds of good quality, evidences of

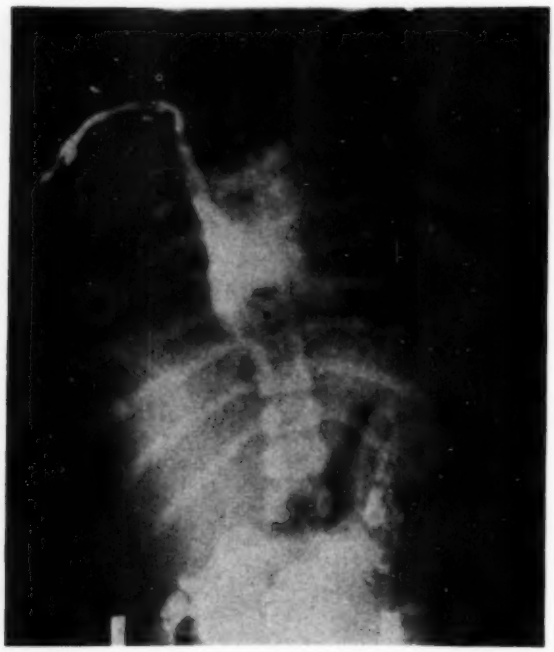

Fig. 3.—Film four seconds after injection of contrast medium, outlining cardiac chambers and pulmonary arteries and demonstrating a large opacity outside the limits of the right ventricle and pulmonary artery.

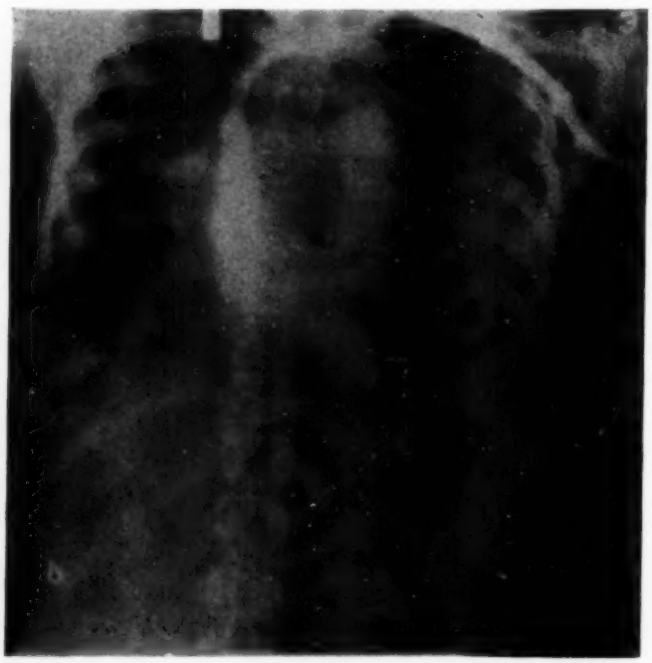

Fig. 4.—Film four seconds after injection of contrast medium, outlining right ventricle and pulmonary arteries and demonstrating a large opacity outside the limits of the right ventricular chamber and pulmonary artery.

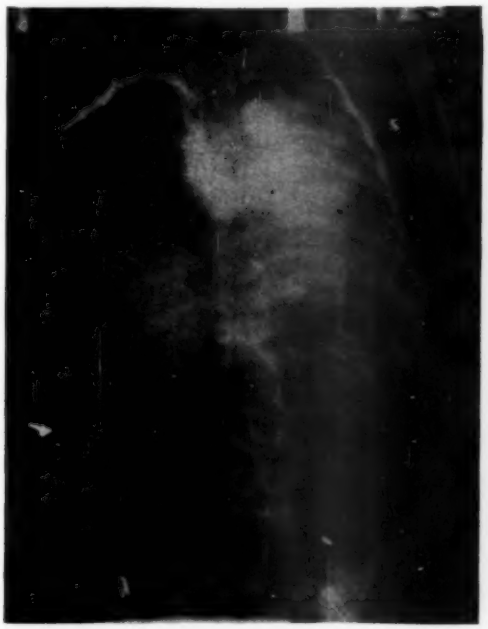

Fig. 5.—Film five seconds after injection of contrast medium, outlining right ventricle and pulmonary arteries and demonstrating a large opacity extending outside the limits of the right ventricular chamber. The pulmonary vessels are filled with contrast medium.

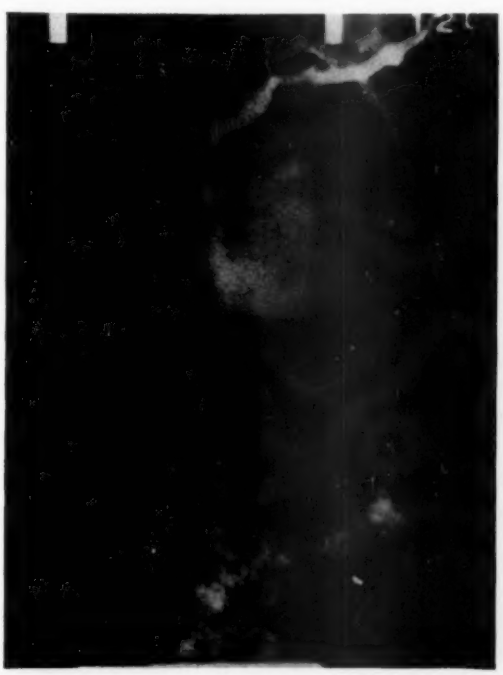

Fig. 6.—Film three seconds after injection of contrast medium, outlining the right ventricular chamber and pulmonary arteries and demonstrating a large opacity outside the limits of the right ventricular chamber. The outlines of the cardiac shadow on the right are obscured due to purposeful overexposure of the film.

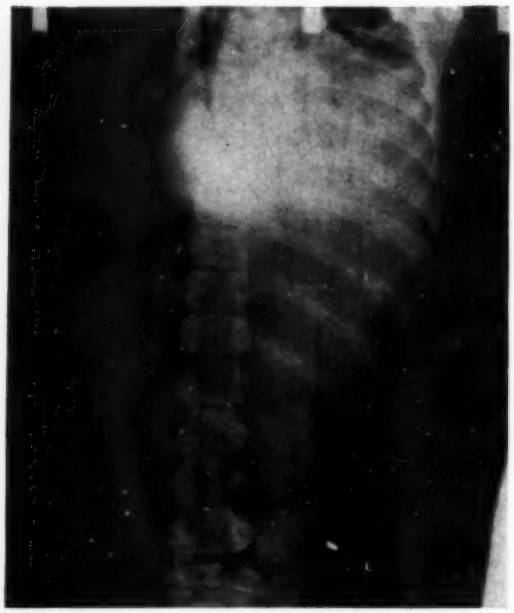

Fig. 7.—Film four seconds after injection of contrast medium, outlining the right ventricular chamber and demonstrating a large opacity outside the limits of the right ventricular chamber.

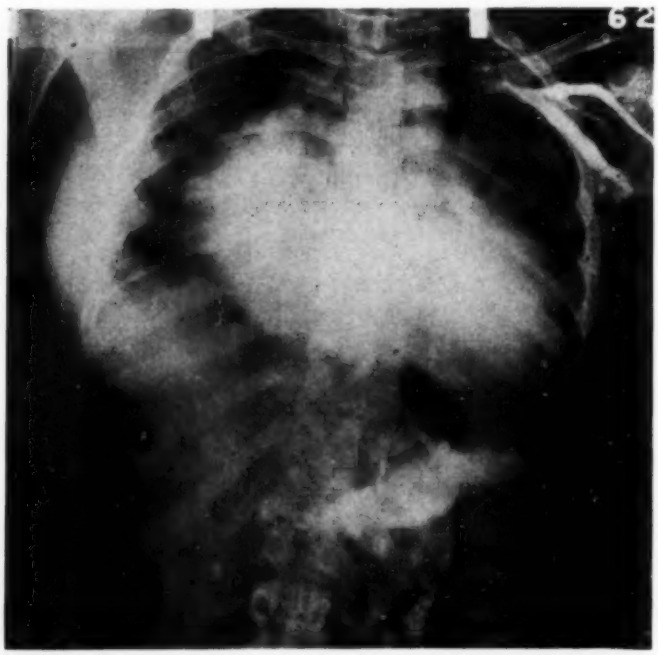

Fig. 8.—Film nine seconds after injection, demonstrating contrast medium in markedly enlarged right and left ventricles. The aorta is visualized.

mitral valvulitis, and physical and roentgenological evidences of a markedly enlarged heart with decreased pulsations of the cardiac borders. Angiocardiography confirmed the presence of an opacity outside the limits of the cardiac chambers (Fig. 7). She responded well to salicylate therapy and did not require a pericardial tap.

CASE 8.—D. C., a Negro woman, 18 years old, was admitted to Charity Hospital on May 23, 1950, with chief complaints of aching precordial pain and progressively increasing dyspnea on exertion for the past seven months. There was no history suggestive of rheumatic fever. She had one child 17 months of age. Physical examination revealed a temperature of 100.2° F., blood pressure of 136/120 mm. Hg, distended neck veins, clear lung fields, marked cardiac enlargement, systolic and diastolic apical murmurs, and hepatomegaly.

Laboratory work revealed negative 1-10,000 tuberculin, negative Kline, venous pressure in right arm 180 mm. of water, electrocardiogram showing right bundle branch block, multiple x-ray views of the chest and fluoroscopy showing marked cardiac enlargement to the right and left. Cardiac catheterization revealed no left-to-right shunt and elevated right atrial, right ventricular, and pulmonary artery pressure; arterial oxygen studies revealed no right-to-left shunt; the atrioventricular oxygen difference was 6.7 volumes per cent. An angiocardiogram (Fig. 8) revealed marked right and left ventricular dilatation with hypertrophy of the right ventricle.

The final diagnosis on this case was acute rheumatic carditis superimposed on chronic rheumatic mitral valvulitis.

DISCUSSION

Steinberg and co-workers[1,2] have emphasized the importance of angiocardiograms in the diagnoses of pericardial effusion. Although this relatively simple procedure has been known for many years, it is not often utilized when a large cardiac shadow presents a diagnostic problem.

A relatively small amount of contrast medium is required, especially in children. Visualization of only the right heart chambers is necessary to confirm or rule out the presence of pericardial effusion. Ten cubic centimeters of contrast medium adequately outlined the right side of the heart in one case. Complicated roentgenologic apparatus is not necessary to obtain diagnostic films, since only one or two pictures are required to outline the right cardiac chambers. If the possibility of superior mediastinal obstruction exists, then the contrast medium may be injected into the saphenous vein with good visualization of the cardiac chambers.[3]

Pericardial effusion is usually associated with the classical signs of cardiac compression; however, there are instances (Case 2) in which a considerable collection of fluid in the pericardial sac does not produce typical symptoms and signs to suggest its presence. Conversely, a dilated heart may result in symptoms and signs which closely simulate the findings associated with a pericardial effusion (Case 8). These are the types of cases in which angiocardiography is of great value. Angiocardiograms outline the limits of the cardiac chambers; however, the presence of a considerable shadow outside of the limits of the cardiac chambers does not necessarily indicate the presence of a pericardial effusion. In one case this was proved at autopsy to be due to an organized, fibrinous, pericardial exudate which did not yield fluid when pericardiocentesis was attempted. Small amounts of fluid usually cannot accurately be demonstrated by angiocardiography.

The angiocardiographic picture in the presence of cardiac hypertrophy is rarely confused with pericardial effusion, since simple hypertrophy does not result in a considerable increase in the size of the cardiac silhouette.

SUMMARY

Eight cases are presented, demonstrating the usefulness of angiocardiography in confirming or ruling out the presence of a pericardial effusion.

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SOME FACTORS AFFECTING THE CLEARANCE OF Na^{24} FROM HUMAN MUSCLE

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SINCE the report by Kety[1] that the local clearance of radioactive sodium (Na^{24}) could be used as an indirect measure of effective blood flow, there have been several reports concerning the use of this technique. Kety theorized that the rate of clearance of radiosodium from tissue in man would be proportional to the amount at the site, and therefore a plot of the activity above the injection site as a function of time would be a straight line. He attempted to verify his hypothesis with a series of experiments in the gastrocnemius muscle of human subjects. Franke and associates[2] ran a series of experiments similar to those of Kety, but for longer intervals of time, and found that the clearance slope was not a straight line if followed for time periods of twenty to sixty minutes. The authors in a previous report[3] have confirmed this finding of Franke but indicated that this finding was not inconsistent with Kety's theoretical presentation.

This report undertakes to explain how these two findings are consistent with each other and to offer a technique for more accurate determinations of the clearance of radiosodium from the muscle in man.

METHOD

The subjects for these experiments were hospitalized male patients, 20 to 45 years of age, who had normal peripheral and central circulations. In all studies the subject was allowed to rest in the prone or supine position for ten to twenty minutes before the experiment was begun. The temperature of the laboratory was maintained between 75° and 80° F., and an attempt was made to measure the clearance rate of each individual at approximately the same time of day.

In each experiment, between 0.05 and 1.0 c.c. of isotonic sodium chloride solution containing 1 to 3 microcuries of Na^{24} was injected. The skin injections were made with a 26 gauge needle, and a bleb was raised. In subcutaneous tissue studies a 26 gauge needle was used, care being taken to penetrate the lowest layer of skin overlying the gastrocnemius muscle and to remain above the muscle with the needle point. All muscle study injections were made into the belly of the gastrocnemius muscle; in most of these experiments a 20 gauge, 1½ inch needle and in a few experiments a 23 gauge, 1 inch needle which was inserted to the hilt were used.

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In every experiment, a thin, mica window Geiger counter was placed in position, and counting was begun between sixty and ninety seconds after the injection was made.

Several series of muscle studies were done, the conditions of the experiment varying in one respect in each series. In series 2 and 3, prior to positioning the counter, the needle while in situ was washed out with 0.9 and 0.2 c.c. of isotonic salt solution, respectively. In series 1, 2, 3, and 4 the counter was placed directly over the site of injection. In series 5 the counter was placed in such a manner that its long axis and that of the needle formed an acute angle varying between 45 and 90 degrees with the counter pointing toward the injected depot. In series 6, the same individuals were tested using the methods in series 1 and 5 alternately. In series 7, the same method as that of series 5 was used except that a 23 gauge, 1 inch needle was used. In all other muscle studies a 20 gauge, 1½ inch needle was used.

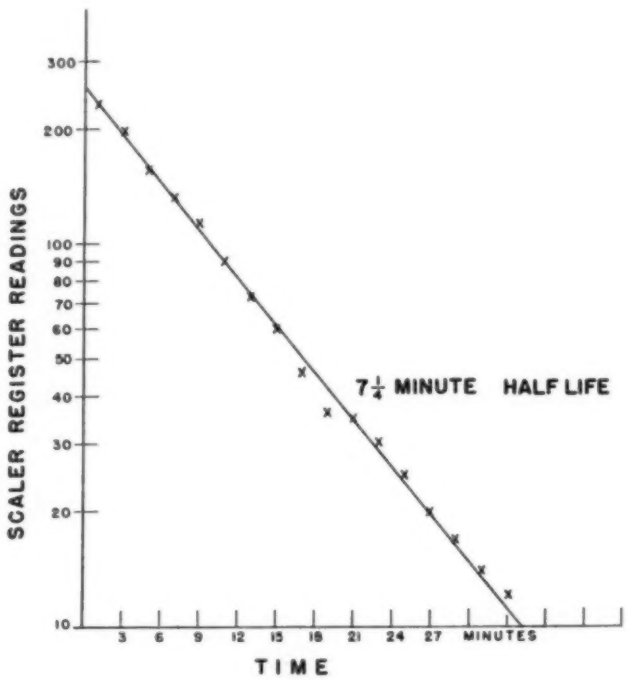

Fig. 1.—Clearance of radioactive sodium (Na^{24}) from skin overlying the gastrocnemius muscle in a normal subject.

After injection and placement of the counter, the activity present was recorded using a scaling circuit with scale selections at 16, 32, 64, and 128. Serial readings were recorded at intervals of two minutes for an hour by means of an automatic printer.

CALCULATIONS

The raw data were plotted on semilogarithmic graph paper as a function of time. In the experiments measuring clearance from skin and in those in sub-

cutaneous tissue, the raw data revealed straight line slopes made up of a single component (Figs. 1 and 2). In experiments involving muscle clearance, the raw data plot revealed a curve consisting of two components (Fig. 3). The second component was a straight line and therefore could be extrapolated back, and pointwise subtraction from the raw data could be performed. The resultant data when plotted were then a straight line (Fig. 4).

The clearance half life is the time taken for the activity initially present to be reduced to one-half. The clearance constant (K) is equal to the natural logarithm of two divided by the clearance half life: $K = \frac{0.693}{T\ \frac{1}{2}}$.

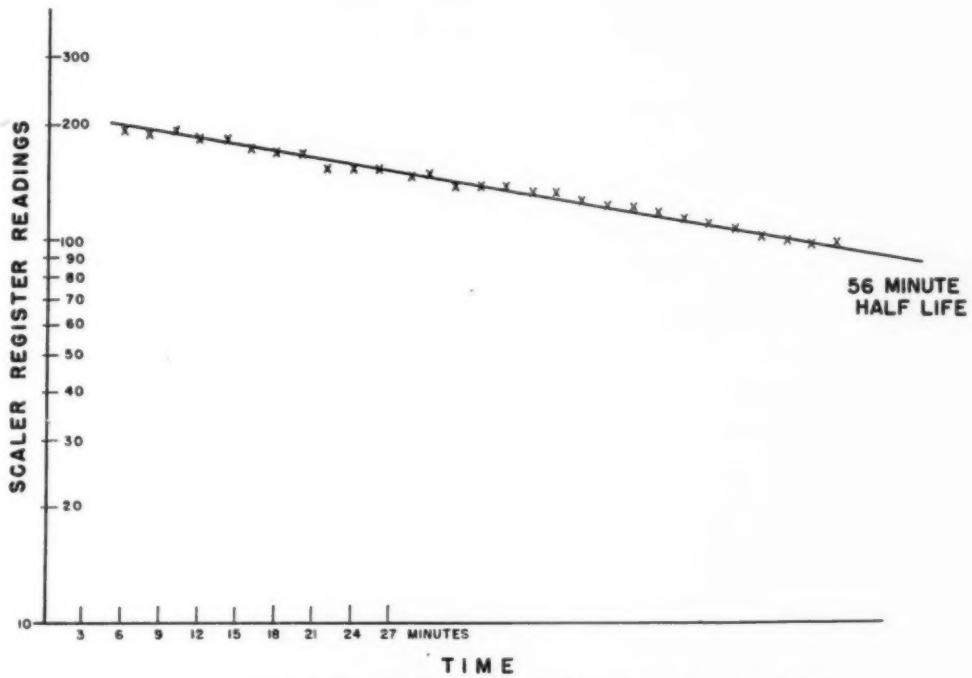

Fig. 2.—Clearance of radioactive sodium (Na^{24}) from subcutaneous tissue overlying the gastrocnemius muscle in a normal subject.

RESULTS

In twenty-two studies of clearance of radiosodium from the skin over the gastrocnemius muscle on twenty subjects, the raw data revealed, when plotted, a straight line in every case. The clearance constants varied from 0.0840 to 0.1582 $minute^{-1}$, and the average clearance constant was 0.0990 $minute^{-1}$.

In six studies of clearance of Na^{24} from subcutaneous tissue, the raw data plot was a straight line in every case, showing a single component. The clearance constant average was 0.014 $minute^{-1}$.

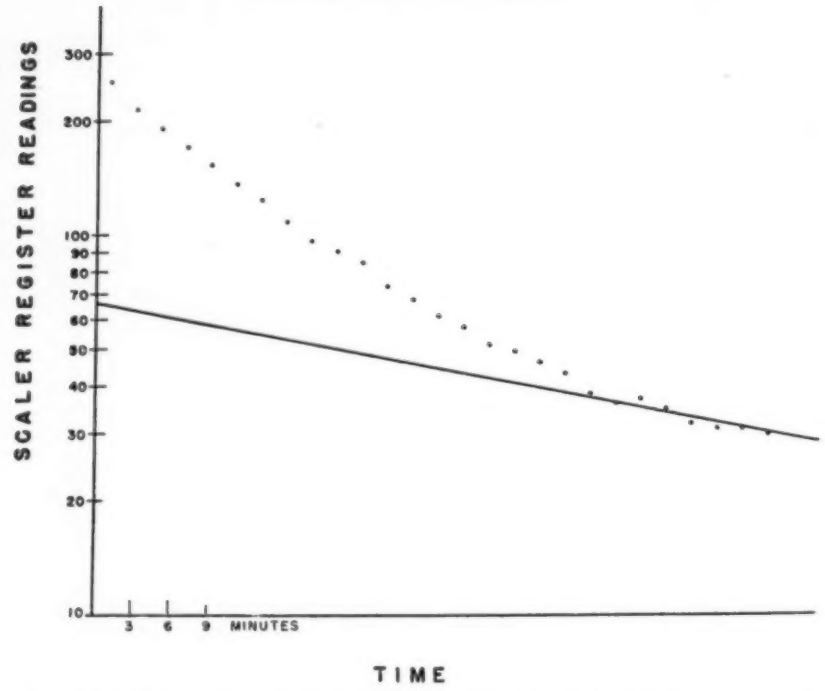

Fig. 3.—Muscle clearance: a graph of the raw data showing two components with the second component extrapolated back to the time of the initial count.

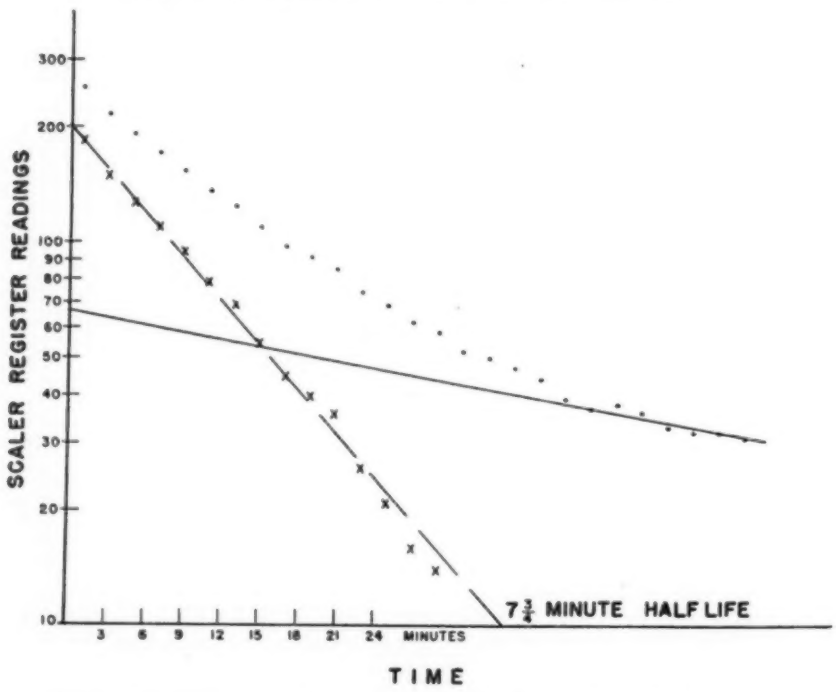

Fig. 4.—Muscle clearance: the second component (subcutaneous tissue clearance) has been extrapolated back to the time of the initial count. Pointwise subtraction of this activity from the raw data has been performed. The result is the clearance curve for muscle tissue alone. This resultant curve is shown by the interrupted line.

In the first series of muscle experiments the counter is placed directly over the site of injection of 0.1 c.c. of isotonic labeled sodium chloride. The raw data, when plotted, revealed a curve clearly consisting of at least two components (Fig. 2). We believe that the second component represents Na^{24} being cleared from subcutaneous tissue which was deposited there as the needle was withdrawn after injection. The second component is a straight line if the last 8 to 10 points are used in drawing the line and can be extrapolated back, thus determining the amount of radioactivity present in the first fifteen to thirty minutes due to the Na^{24} in the subcutaneous tissue. If this activity is then subtracted pointwise from the original raw data, the activity resulting from Na^{24} in muscle tissue alone is determined. When this net activity is plotted on semilogarithmic paper, a straight line can be drawn through the points.

In this series of experiments thirty-six different individuals were tested, and a total of sixty-three tests was run. The clearance constant for muscle varied considerably from individual to individual, ranging from 0.0757 to 0.1540 minute^{-1}. The average clearance constant was 0.1092 minute^{-1}, and the average percentage of activity present in the second component at the moment of recording the initial count was 44 per cent.

In five subjects in this series on whom the experiment was repeated three times, the reproduction range predicted from the formula, range = 2 × standard deviation, varied from 7 to 29 per cent (see Table I).

TABLE I. REPRODUCTION WITH COUNTER DIRECTLY OVER INJECTION SITE (SERIES 1)

	CLEARANCE CONSTANT (K) (MINUTE^{-1})	AVERAGE CLEARANCE CONSTANT (K) (MINUTE^{-1})	HALF LIFE (MINUTES)	AVERAGE HALF LIFE	RANGE (2 × STANDARD DEVIATION)	RANGE (2 × STANDARD DEVIATION) (%)	% IN SUBCUTANEOUS TISSUE AT INITIAL COUNT	AVERAGE % IN SUBCUTANEOUS TISSUE AT INITIAL COUNT
A	(1) 0.1260		5.5				37.4	
	(2) 0.1026	0.1249	6.75	5.5	0.0880–0.1507	27.3	38.2	37.1
	(3) 0.1462		4.75				35.9	
B	(1) 0.1155		6.0				42.7	
	(2) 0.1385	0.1202	5.0	5.75	0.0958–0.1446	20.3	57.8	47.4
	(3) 0.1065		6.5				41.6	
C	(1) 0.1110		6.25				42.1	
	(2) 0.0867	0.1079	8.0	6.4	0.0775–0.1383	29.0	47.5	45.9
	(3) 0.1260		5.5				48.2	
D	(1) 0.1066		6.5				39.1	
	(2) 0.0924	0.1019	7.5	6.75	0.09887–0.1151	13.0	48.2	43.5
	(3) 0.1066		6.5				43.2	
E	(1) 0.1458		4.75				47.7	
	(2) 0.1540	0.1535	4.5	4.2	0.1413–0.1657	7.3	52.8	43.7
	(3) 0.1606		4.0				30.6	

In series 2, the procedure was the same as in series 1 with the exception that the needle was washed out with 0.9 c.c. of isotonic salt solution while the needle was in the muscle. Seven experiments were performed on five different subjects.

The raw data showed approximately a straight line; the clearance constant approached that found for injections of Na^{24} made directly into subcutaneous tissue. The average clearance constant in this series was 0.0330 $minute^{-1}$.

In series 3 the procedure was identical with that in series 2 with the exception that 0.2 c.c. of isotonic salt solution was used in washing out the needle. Seven experiments were performed in this series. The raw data showed curves essentially the same as those found in series 1. The average clearance constant was 0.1025 $minute^{-1}$, and the average percentage of activity in subcutaneous tissue at the initial count was 38 per cent.

In series 4 the procedure was the same as in series 1 with the exception that 1.0 c.c. of Na^{24} in isotonic salt solution was injected into the muscle instead of 0.1 c.c. of Na^{24}. Five experiments were performed in this series. The raw data revealed curves identical with those found in series 1. The average clearance constant was 0.1059 $minute^{-1}$. The percentage of activity in subcutaneous tissue at the moment of initial count was 64 per cent.

In series 5 the procedure was the same as in series 1 with the exception that the counter was placed at an acute angle to the path of injection. Twenty-one different individuals were tested, and a total of thirty-eight experiments was performed in this series. The clearance constant varied considerably from individual to individual, ranging from 0.0750 to 0.1319 $minute^{-1}$. The average clearance constant was 0.0983 $minute^{-1}$, and the average percentage of activity in subcutaneous tissue at the moment of initial count was 32 per cent, somewhat lower than in series 1.

In five subjects in this series on whom the experiment was repeated three times, the reproduction range predicted from the formula, range $= 2 \times$ standard deviation, varied from 5.7 to 19.4 per cent (see Table II).

In series 6 the procedure was identical with the procedures used in series 1 and 5, and they were used alternately on the same individual. Three subjects were used, and a total of six experiments was performed. In the comparison of the two methods in all three subjects, the results showed clearance constants to be much the same with a difference in the percentage of activity in subcutaneous tissue at the initial count. The method used in series 5 showed a smaller percentage of subcutaneous activity as compared to the method of series 1, the differences in each individual ranging from 8 to 23 per cent.

In series 7 the procedure was the same as that in series 1 with the exception that a 23 gauge, 1 inch needle was used. Four such experiments were performed, and the results were identical with those found in series 1 as to clearance constant and percentage of subcutaneous activity.

The clearance constants determined in series 1 and 5 were averaged, and the standard deviation was determined. The average clearance constant was 0.1061 $minute^{-1}$, and the standard deviation was 0.0214 $minute^{-1}$. The predicted range for the formula (range $= 2 \times$ standard deviation) was 0.0633 to 0.1489 $minute^{-1}$. In 101 experiments, only two clearance constants were not within this range. On the basis of statistical considerations the probability of determinations lying outside the predicted range is 5 per cent.

TABLE II. REPRODUCTION WITH COUNTER AT AN ANGLE TO AXIS OF INJECTION (SERIES 2)

	CLEARANCE CONSTANT (K) (MINUTE^{-1})	AVERAGE CLEARANCE CONSTANT (K) (MINUTE^{-1})	HALF LIFE (MINUTES)	AVERAGE HALF LIFE	RANGE (2 × STANDARD DEVIATION)	RANGE (2 × STANDARD DEVIATION) (%)	% IN SUBCUTANEOUS TISSUE AT INITIAL COUNT	AVERAGE % IN SUBCUTANEOUS TISSUE AT INITIAL COUNT
A	(1) 0.0792		8.75				24.0	
	(2) 0.0750	0.0764	9.25	9.1	0.0726–0.0802	5.7	19.8	26.5
	(3) 0.0750		9.25				35.6	
B	(1) 0.0894		7.75				17.3	
	(2) 0.1026	0.0948	6.75	7.3	0.0834–0.1062	12.0	26.4	22.7
	(3) 0.0924		7.5				24.4	
C	(1) 0.0991		7.0				49.5	
	(2) 0.0991	0.1062	7.0	6.5	0.0856–0.1268	19.4	44.8	49.4
	(3) 0.1205		5.75				54.0	
D	(1) 0.1155		6.0				60.8	
	(2) 0.1026	0.1046	6.75	6.6	0.0928–0.1164	11.8	50.5	50.5
	(3) 0.0956		7.25				40.2	
E	(1) 0.0770		9.0				29.0	
	(2) 0.0816	0.0772	8.5	9.0	0.0700–0.0844	9.8	39.4	32.2
	(3) 0.0730		9.5				28.2	

DISCUSSION

It has been shown previously that the decrease in activity in tissue per unit time is proportional to the activity present.[1,3] If the radioactivity present is plotted on semilogarithmic graph paper as a function of time, the plotted points should be along a straight line. In experiments measuring the clearance of radiosodium from skin and subcutaneous tissue, the plotted points were along a straight line. However, if Na^{24} is deposited in two or more different types of tissue with different rates of clearance, a plot of the raw data gives a curve which can be resolved into two or more linear components.

The total counting rate when the muscle clearance is determined consists of the following factors: (1) the natural background of the counter, (2) the counting rate resulting from the dispersal of Na^{24} throughout the body via the vascular system, (3) the counting rate resulting from Na^{24} spilled on the skin, (4) the counting rate resulting from Na^{24} going into cells and being fixed there temporarily, (5) the counting rate resulting from Na^{24} deposited in subcutaneous tissue when the needle is withdrawn after the injection has been made, and (6) the counting rate of Na^{24} in the muscle.

The fact that injections made into the skin show backgrounds varying from 0.5 to 5.0 per cent of the initial activity (providing no Na^{24} is on the skin) and, when plotted, show a straight line indicates that the first four factors are small and no correction need be made for them.

Factor 5 is of significance since it has been shown that clearance of Na^{24} from subcutaneous tissue is markedly slower than the clearance of the same material from skin and muscle.[2,4] Our own work has confirmed these findings.

The amount of Na^{24} in subcutaneous tissue when recording of activity is begun (approximately one and one-half minutes after the injection in these experiments) is an average of 37 per cent, an appreciable percentage of the initial counting rate. After a short interval, the activity resulting from Na^{24} in the muscle has decreased considerably, and, although the activity resulting from Na^{24} in subcutaneous tissue has also diminished during this time, the rate of decrease has been much slower. Consequently, after ten to twelve minutes, the largest percentage of the activity "seen" by the counter is a result of the Na^{24} in subcutaneous tissue. If the experiment is run for a long enough time so that the amount of activity resulting from Na^{24} still in muscle has become very small (the plotted curve has become a straight line), the clearance curve for material in subcutaneous tissue is determined. The clearance curve can be extrapolated back so that the activity due to the Na^{24} in muscle tissue alone can be determined by pointwise subtraction from the raw data the activity resulting from Na^{24} in the subcutaneous tissue.

It should be noted that the clearance constants for subcutaneous tissue obtained from these data agree closely with those clearance constants determined by injecting directly into subcutaneous tissue. Further, by placing the counter in different positions in relation to the axis of the injecting needle, it is possible to note different percentages of initial activity present in subcutaneous tissue. However, when extrapolation is carried out, the values of the clearance constants from the muscle tissue agree very closely. If two counters are used and placed in different positions so that one counter will "see" less of the material in the subcutaneous tissue, the raw data will appear dissimiliar, but when treated as described above, the clearance constants found for the subcutaneous tissue and muscle will agree very closely.

We have found, using our technique in normal subjects, that the experiment should be run for about one hour to find the clearance curve for subcutaneous tissue.

In series 2 and 3 an attempt was made to lessen the amount of Na^{24} deposited in subcutaneous tissue by diluting the Na^{24} at the tip of the withdrawing needle with isotonic sodium chloride. In series 3, 0.2 c.c. was used with no apparent change in the nature of the curves obtained. In series 2, the needle was washed with 0.9 c.c. of solution. A plot of the activities in this series gave straight lines, but the clearance constants found approached those found for subcutaneous tissue clearance. We believe that the incoming pressure of the additional 0.9 c.c. of isotonic salt solution forced a considerable portion of the Na^{24} initially deposited in the muscle up along the path of least resistance, around the needle into subcutaneous tissue; the clearance of the small percentage of Na^{24} remaining in the muscle tissue is masked, and the resultant clearance rate approaches that for subcutaneous tissue.

In series 4, 1.0 c.c. of isotonic sodium chloride solution containing Na^{24} was injected. We considered it possible that the relative amount of Na^{24} deposited in the subcutaneous tissue by the withdrawing of the needle would be considerably lessened because the needle channel would be relatively small compared to the injected volume. However, the results were almost identical with those of the

experiments in series 1. Apparently, pressure resulting from 1.0 c.c. forces enough solution into subcutaneous tissue to give approximately the same relative proportions of Na^{24} in subcutaneous and muscle tissues as when 0.1 c.c. is used.

In series 5, when the counter was positioned so that it would "see" less of the Na^{24} in subcutaneous tissue, the percentage of initial activity due to material in subcutaneous tissue was smaller. When this method was used, attempts at reproduction of curves in the same individual showed a narrower range than similar experiments in which the method of series 1 was used. We intend to use this method in future studies of muscle clearance.

Mufson,[5] in a recent report, suggested that injection into a muscle might cause local spasm, thus interfering with the normal clearance of radiosodium. We have noticed a flat curve which we attribute to spasm appearing in about 35 per cent of the subjects studied. However, such spasm invariably disappears between two and six minutes after counting is begun. This was determined by studying the graph of the raw data and assuming that spasm was no longer present when the slope of the curve became much more acute. In plotting the final clearance curve in cases where there appeared to be spasm, the points during spasm were ignored. In repeated studies on the same individual, spasm was not always present, but, in spite of this, the clearance constants were in close agreement.

Because of this frequent occurrence of spasm, each study done with this technique must be continued for a period of about one hour.

Elkin and Cooper[3] have expressed the values for the clearance of radiosodium from the muscle in terms of the percentage of initial activity at the end of ten minutes following the initial count. This method does not give a true evaluation of the effective blood flow in muscle because it takes no account of the effect of spasm nor of the activity due to the Na^{24} deposited in subcutaneous tissue.

Franke and associates,[2] because they noted a curve in plotting the clearance of radiosodium from muscle, reported clearance times as the time taken to reach one-half the activity initially present, disregarding the slope. The same objections hold for this method as for that of Elkin and Cooper.

There have been two recent reports by British investigators[7,8] using the clearance of radiosodium (Na^{24}) from human muscle technique. Both of these reports suggested that the method did not measure changes in blood flow. The first report based its conclusion on the finding that Na^{24} clearance did not show an increase when Adrenalin was given intravenously at the rate of 10 μg per minute. The second of these reports found that resting clearance curves in subjects with normal and abnormal circulations were not different and that exercise did not uniformly produce an increased clearance, although it did do so in the majority of their cases.

Both of these investigators used needles 2 cm. in length, which the authors have found, on the basis of unpublished data, to be too short to reach muscle tissue in many robust individuals. In the first report, the original work by Allen, Barcroft, and Edholm[9] was referred to which showed that Adrenalin given intravenously at a rate of 10 μg per minute would result in an increase in muscle blood flow. The maximum increase of flow persisted for only two minutes. However,

from then on for the duration of the infusion, the increase in blood flow was about 50 per cent above preinfusion levels. The marked increase persisting only for two minutes will not be shown by the radiosodium clearance technique. No explanation can be offered for not finding an increase in effective blood flow plateau during the intravenous administration of Adrenalin. However, in the one graph shown by the investigator, if the least square method is used to determine the clearance slopes before and during infusion, the results seem to indicate such an increase.

In the second report a resting clearance was first determined for ten minutes, and then exercises were performed and again a clearance was determined for ten minutes. This procedure will result in erroneous conclusions for two reasons. First, taking readings for only ten minutes may give a curve far too flat if any spasm occurs following the injection. Second, after exercise, when the blood flow has increased considerably, most of the radioactivity being recorded is resulting from sodium in subcutaneous tissue since the Na^{24} in muscle tissue has already been cleared for the most part.

SUMMARY

1. The clearance curve of Na^{24} from skin is a straight line when plotted on semilogarithmic paper.

2. The clearance curve of Na^{24} from subcutaneous tissue is a straight line when plotted on semilogarithmic paper, although clearance is much slower than in skin.

3. The clearance curve of Na^{24} from muscle is a straight line. However, when the raw data are plotted on semilogarithmic graph paper, it appears to be a curve because it is a resultant of clearance from subcutaneous and muscle tissue.

4. A method of determining clearance of Na^{24} from muscle alone has been suggested.

The authors wish to thank Dr. B. Roswit, Director of the Radioisotope Unit, and the members of the staff of the Unit whose cooperation made this work possible. We also wish to thank the Medical Illustration Service of the Bronx Veterans Hospital for preparing the figures used in this article.

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CLINICAL AND CARDIAC CATHETERIZATION FINDINGS COMPATIBLE WITH EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE: A REPORT OF TWO CASES

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TWENTY-TWO cases of Ebstein's anomaly of the tricuspid valve have been reported.[1] However no case has been diagnosed during life. The results of clinical investigation including venous catheterization of the heart have led us to consider this diagnosis in two patients. The findings seem of sufficient interest to present despite the lack of autopsy confirmation.

CASE 1.—M. H., a white woman 22 years of age, complained of breathlessness and palpitations.

The mother could not recall any illness during the pregnancy, which was her first, and the labor was normal. A murmur over the heart was heard soon after birth, but there was no cyanosis. The child's development was normal until breathlessness on exertion developed at the age of 5 years. This has not increased in severity since that time, and she is able to cycle to work and can dance a little without undue distress. Palpitations, described as "missed beats," have occurred after effort, but do not disturb her. Blueness of the face and hands have also been noted by the patient after exertion and during cold weather for as long as she can remember.

Rheumatic fever was diagnosed at the ages of 2, 6, 11, and 16 years. At those times she had a pyrexial illness accompanied by swollen and painful joints and spent from weeks to months in bed. At the end of July, 1950, she developed a pyrexia with cough, and during the following seven months she had four similar attacks. She was admitted to the Johannesburg General Hospital on Feb. 7, 1951, for investigation for a possible case of subacute bacterial endocarditis.

Physical Examination.—The patient was a well-nourished, normally developed, young white woman. The fingers were long and showed slightly increased curvature of the nails but no clubbing. Cyanosis was not detected. The sternum was moderately depressed. The examination disclosed an enlarged spleen. The remainder of the physical examination was normal except for the findings in the cardiovascular system.

The pulse rate was regular. The arterial pulses were equal in both arms and were present in the lower extremities. The blood pressure was 110/90 mm. Hg. The jugular venous pressure and pulsations were normal (Fig. 1). The apex beat could not be felt, and there was a slight diffuse pulsation of the intercostal spaces to the left of the sternum. A soft systolic murmur was

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heard over the pulmonary and mitral areas as well as down the left sternal border. The second sound at the base of the heart was single and unsplit. A mid-diastolic murmur was present at the mitral area and to the left of the sternum (Fig. 1).

Investigations.—Fluoroscopic examination in the posteroanterior view showed an enlarged heart predominantly to the left. The cardiothoracic ratio was 62 per cent. The heart borders showed diminished pulsation. The aorta descended normally on the left side. A concavity was present in the left pulmonary artery region (pulmonary conus) (Fig. 2). The left heart border below the level of the pulmonary artery was prominent, giving rise to a square-shaped heart.

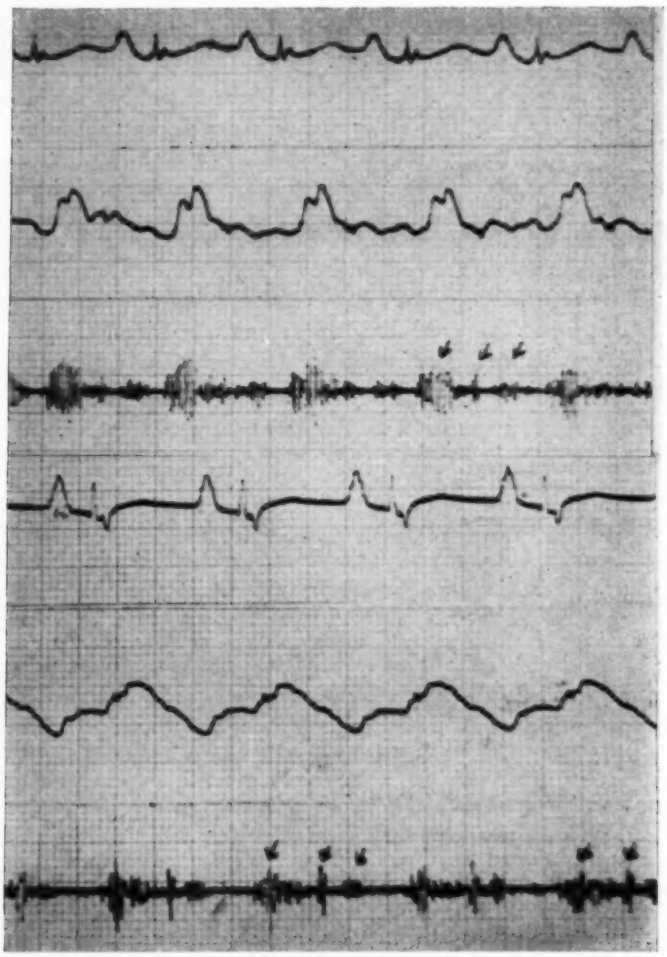

Fig. 1.—The electrocardiogram (Lead II), the jugular phlebogram, and the heart sounds (third and fourth intercostal spaces to left of sternum) in Case 1 (upper three tracings) and in Case 2 (lower three tracings). Both sets of simultaneous recordings show prominent P waves and prolonged QRS complexes in the electrocardiogram, absence of tricuspid incompetence in the phlebogram, and systolic and mid-diastolic murmurs in the phonocardiogram.

The lungs appeared to be normally vascularized. An end-on view of a pulmonary vessel in the lung field as well as the fleck pulmonale in the right anterior oblique view showed pulsations. The right ventricle was flattened against the sternum in both oblique views and was considered to be markedly enlarged. The left ventricle contracted vigorously in the left anterior oblique view.

These pulsations contrasted markedly with the relatively immobile borders in the posteroanterior view, and it was concluded that the right ventricle formed the left heart border in this view. The left auricle was not enlarged, and the lung fields were normally vascularized.

Electrocardiogram.—Low voltage was present in all leads (Fig. 3). The QRS complex measured 0.12 second in the standard leads. The findings were consistent with right bundle branch block.

Additional Laboratory Investigations.—Repeated blood cultures were negative. The erythrocyte sedimentation rate was 6 mm. in 1 hour (Westergren). The blood count was normal. Circulation times were: arm to tongue (Decholin) 19 seconds, arm to lung (ether) 8.3 seconds.

Cardiac Catheterization.—A No. 6 cardiac catheter was introduced into the median basilic vein of the left forearm and passed into the right pulmonary artery. Pressures and blood samples for oxygen analysis were taken from the pulmonary artery, right ventricle, right auricle, and superior vena cava (Table I).

TABLE I.

SITE	OXYGEN CONTENT (VOL. PER CENT)	SATURATION (PER CENT)	PRESSURES (MM. Hg)	
			SYSTOLIC/ DIASTOLIC	MEAN
Right pulmonary artery	17.04	81.4		
Main pulmonary artery	17.0	81.0	22/10	14
Main pulmonary artery	16.5	78.7		
Right ventricle (distal)	16.7	79.8	22/4	10
Right ventricle (proximal)	16.01	76.0	7/4	5.0
Right auricle (low)	16.43	78.2		
Right auricle (high)	14.83	70.9	7/4	5.0
Right auricle (high)	13.18	63.0		
Superior vena cava	12.01	57.4		
Superior vena cava	11.37	54.3		
Femoral artery	18.3	87.0		

Reference level for pressure readings was 5 cm. posterior to the angle of Louis.

Oximetry.—The resting arterial oxygen saturation measured by an oximeter* was 87 per cent. This rose to 94 per cent at the end of one minute of voluntary hyperventilation (maximum breathing capacity). A standard exercise test (stepping up a 9 inch step thirty times in one minute) resulted in a drop in the arterial saturation from 87 to 76 per cent. Oxygen administration for five minutes caused a rise in arterial oxygen saturation from 90 per cent to 96 per cent.

CASE 2.—Patient I. D. was a 20-year-old white woman whose complaints were breathlessness on exertion and cyanosis since the age of 6 years. She was the youngest child of a family of ten. The mother could not recall any illness during the pregnancy, and the birth and the early development of the patient had been normal.

An acute episode of diarrhea and vomiting at the age of 6 years preceded the onset of breathlessness on exertion and cyanosis, both of which became progressively more noticeable. In 1949, she failed to regain consciousness for one hour following a tooth extraction under general anesthesia, and two weeks later she had a similar but shorter period of unconsciousness followed by substernal pain. Cyanosis and breathlessness on exertion had increased following these episodes.

The effort tolerance at present is limited to the ascent of about six steps before breathlessness becomes noticeable. Palpitations have occurred frequently during the last few years.

*Waters-Conley absolute reading oximeter.

Fig. 2.—Posteroanterior, right, and left anterior oblique views of the chest in Case 1.

Physical Examination.—General body development was normal. Marked cyanosis and clubbing of the fingers and toes were present. The pulse was regular, equal in both arms and palpable in the legs. The blood pressure was 108/80 mm. Hg. The jugular venous pressure and pulsations were normal (Fig. 1). No deformity of the chest was noted and the apex was palpated in the sixth intercostal space just beyond the mid-clavicular line. Thrills were not felt, but a soft systolic and low-pitched mid-diastolic murmur were heard at the apex of the heart. A loud systolic and soft mid-diastolic murmur could also be heard in the third and fourth intercostal spaces to the left of the sternum (Fig. 1). A soft systolic murmur and a single unsplit second heart sound were heard at the pulmonary area.

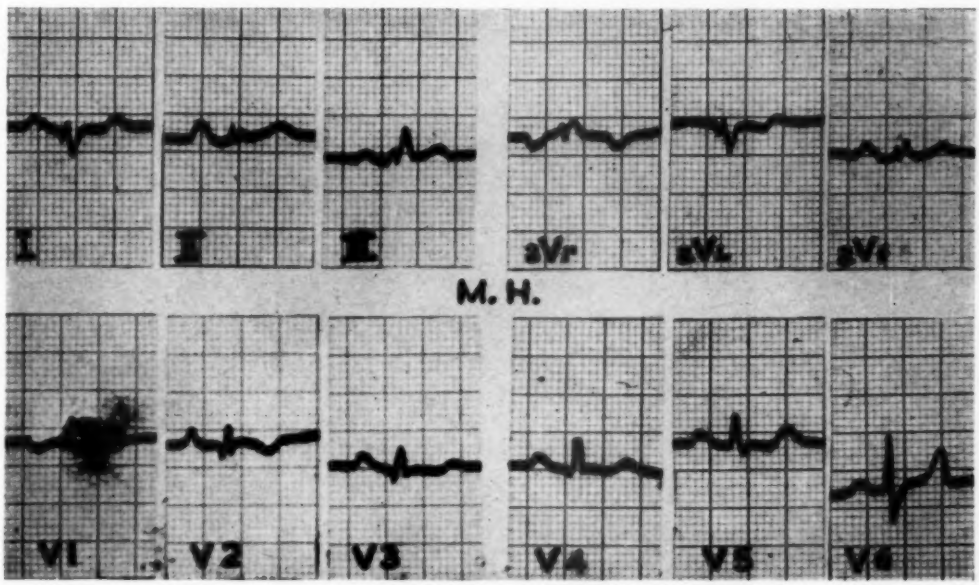

Fig. 3.—Electrocardiogram in Case 1 (retouched).

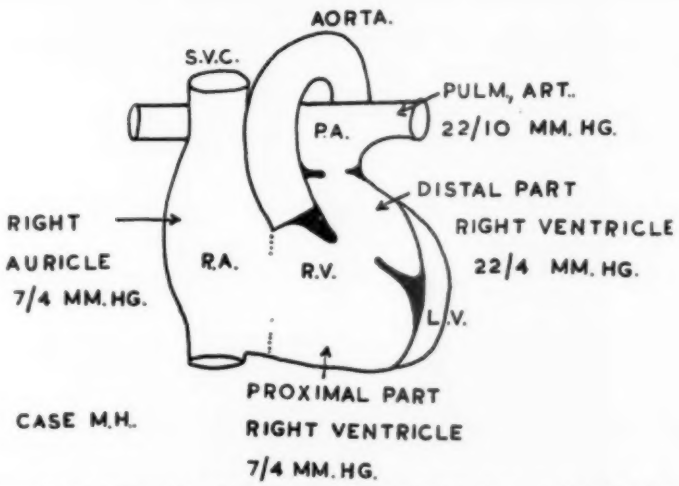

Fig. 4.—A schematic representation of the pressures recorded in Case 1, showing the division of the right ventricle into two distinct pressure zones by a displaced tricuspid valve.

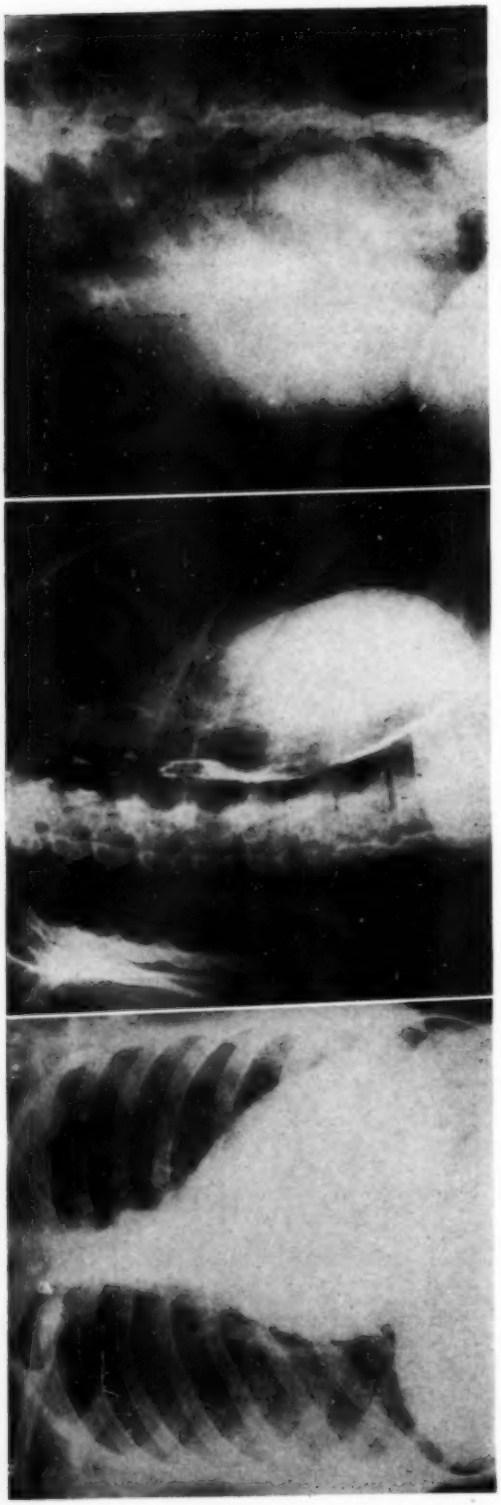

Fig. 5.—Posteroanterior, right, and left anterior oblique views of the chest in Case 2.

Investigations.—Fluoroscopic examination in the posteroanterior view showed a large square-shaped heart (cardiothoracic ratio 64 per cent) (Fig. 5). The lung fields appeared to be well vascularized. The aorta descended normally on the left side. A concavity was present in the region of the left pulmonary artery. The left border of the heart showed a prominence below the usual site of the pulmonary artery. The pulsations of the heart borders in the posteroanterior view were small. Pulmonary artery pulsation was just perceptible. The right ventricle was flattened against the sternum in the oblique views and was considered to be markedly enlarged. The left ventricle pulsated normally in the left anterior oblique view; this contrasted markedly with the pulsations of the remainder of the heart. It was considered that the right ventricle formed the left border of the heart in the posteroanterior view, and this was confirmed during catheterization. Posterior displacement of the left ventricle was assumed to be due to the enlarged right ventricle. There was no left auricular enlargement.

Electrocardiogram.—Right bundle branch block and tall peaked P waves in Leads I, II, aV_F, V_1, and V_2 were present (Fig. 6). A subsequent tracing showed a nodal rhythm with inversion of the P waves in Leads II and III.

Cardiac Catheterization.—A No. 7 cardiac catheter was introduced into the right pulmonary artery via the cephalic vein of the left forearm. Blood samples were taken and the pressures recorded as the catheter was withdrawn from the pulmonary artery to the superior vena cava (Table II).

TABLE II.

SITE	OXYGEN CONTENT (VOL. PER CENT)	SATURATION (PER CENT)	PRESSURES (MM. Hg)	
			SYSTOLIC/ DIASTOLIC	MEAN
Right pulmonary artery	20.3	64.5	22/10	18
Right pulmonary artery	19.3	61.3	22/10	18
Right ventricle (distal)	20.95	66.6	22/8	16
Right ventricle (proximal)	19.3	61.3		9.5*
Right auricle (mid)	19.5	62.1		
Right auricle (high)	18.5	58.9		
Superior vena cava	13.5	43.0		
Femoral artery	21.4	68.3		

*Saline manometer reading was measured in centimeters of saline and converted into millimeters of mercury. Reference level for pressure readings was 5 cm. posterior to the angle of Louis.

Oximetry.—The resting arterial oxygen saturation measured by an oximeter was 69 per cent. This rose to 77 per cent at the end of one minute of voluntary hyperventilation (maximum breathing capacity). The standard exercise test resulted in a drop of 13.5 per cent at the end of one minute, and the administration of 99 per cent oxygen through a mask caused a rise of 14 per cent in the arterial oxygen saturation at the end of five minutes.

DISCUSSION

Engle, Payne, Bruins, and Taussig[1] have reported three cases of Ebstein's anomaly of the tricuspid valve diagnosed at autopsy and have analyzed the clinical syndrome from the findings in these cases and from those reported in the literature. Their conclusions were as follows: "In this malformation the displaced tricuspid valve divides the right ventricle into two parts and thereby causes the proximal portion to be continuous with the cavity of the right auricle.

The anomalous valve is so arranged, however, that it is competent. The myocardium of the right ventricle is congenitally thin. The primary effect of the anomaly is to reduce the efficiency of the right heart. As the upper (proximal) chamber cannot empty itself completely, it enlarges progressively. If the foramen ovale is incompletely sealed, it is opened, and venous blood is shunted from the right auricle into the left auricle and thence into the systemic circulation. The lower (distal) chamber, which receives less than the normal volume of blood, delivers an adequate amount of blood to the lungs for oxygenation."

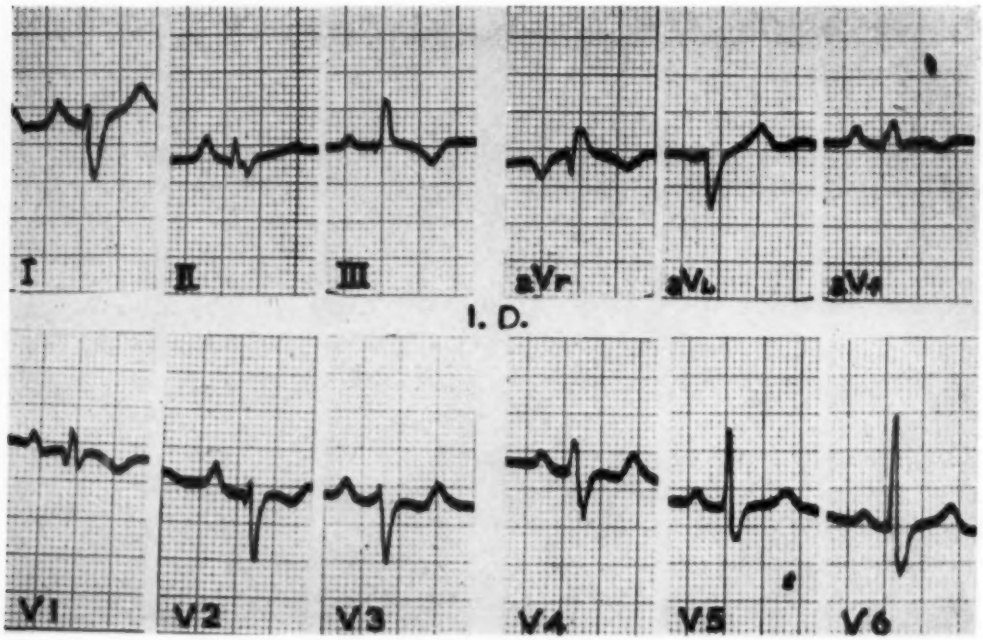

Fig. 6.—Electrocardiogram in Case 2 (retouched).

The possibility of the presence of a displaced tricuspid valve in our two patients was based upon the differences in pressure recorded in the distal and proximal parts of the right ventricle. Case 1 had a pulmonary artery pressure of 22/10 mm. Hg, mean 14 mm. Hg. The pressure in the distal part of the right ventricle was 22/4 mm. Hg, mean 10 mm. Hg, and in the proximal chamber of the right ventricle and right auricle it was 7/4 mm. Hg, mean 5 mm. Hg. It was concluded that the right ventricle was divided into two distinct pressure zones. The similarity of the pressures in the proximal part of the right ventricle and the right auricle was confirmed by a continuous tracing recorded while the catheter was withdrawn from a site well to the left of the spine (i.e., the proximal part of the right ventricle) to a site well to the right of the spine (i.e., the right auricle). Pressures recorded while the catheter was pulled from the pulmonary artery to the right auricle confirmed the above findings and, in addition, demonstrated a distinct drop in pressure in the mid-right ventricle. The pulmonary artery pressure in Case 2 was 22/10 mm. Hg, and in the proximal part of the right ven-

tricle just below the pulmonary valve it was 22/8 mm. Hg. The mean pressures were 18 mm. Hg in the pulmonary artery, 16 mm. Hg in the distal part of the right ventricle, and 9.5 mm. Hg in the proximal part of the right ventricle. The mean pressure was higher in the distal as opposed to the proximal part of the right ventricle, and it was concluded that a displaced tricuspid valve was responsible for this difference.

Arterial unsaturation in one and a marked drop in both patients during the performance of exercise indicated a venous-arterial shunt. That these shunts took place through a defect in the auricular septum was suggested by the following findings: The pressure in the pulmonary artery was lower than the systemic pressure at all times during the cardiac cycle. It is therefore impossible that a reversed shunt through a patent ductus arteriosus could account for the resting or exercise-induced arterial blood unsaturation. A high ventricular septal defect would be associated with a systolic hypertension in the right ventricle. This was not found. The only remaining possibility was a venous arterial shunt through an atrial septal defect. Its presence was suggested by the finding of a higher blood oxygen content in blood from the right auricle than from the superior vena cava. It was concluded that a left-to-right auricular shunt was present and that the only possible venous-arterial shunt capable of explaining the resting and exercise-induced arterial blood unsaturation was a right-to-left auricular shunt.

The pulse contours from the right ventricular cavity were distinctive (Fig. 7). Normally the right ventricular pressure tracing is characterized by a steep rise and fall corresponding to systolic contraction and isometric relaxation, respectively. This contrasts sharply with the plateau diastolic curve which follows. A gradual rise and fall characterized the systolic pressure in the distal part of the right ventricle in both our patients (Fig. 7,*B*). The diastolic plateau was abbreviated. The pressure increase was gradual to begin with and became more abrupt with systolic ejection. The proximal chamber showed only a slow and small rise and a gradual fall, and evidence of the systolic ejection found in the distal chamber was absent (Fig. 7,*C*). The auricular tracing in Case 1 was characterized by a less abrupt descent of the "C" wave than is usual (Fig. 7,*D*). Tricuspid regurgitation was not demonstrated in this auricular tracing or in the jugular phlebogram in both cases (Fig. 1).

The oximeter showed a marked fall in the arterial oxygen saturation during exercise; this was accounted for by the presence of a venous-arterial shunt. The administration of 99 per cent oxygen for five minutes caused a rise in the arterial oxygen saturation in Case 1 from 90 to 96 per cent. This was an essentially normal reaction which was in keeping with the smallness of the shunt at rest (approximately 16 per cent of the venous blood). In Case 2 oxygen inhalation resulted in a rise from 70 to 84 per cent. This is more than double the rise that occurs normally. The failure to become fully saturated in this case was due to the large venous-arterial shunt present at rest (approximately 48 per cent of the venous blood). Voluntary hyperventilation for one minute resulted in an increase in arterial oxygen saturation of 7 and 8 per cent. We have observed that with adequate hyperventilation there is a drop in the arterial blood saturation in

cases of Fallot's tetralogy and Eisenmenger's complex. Pulmonic stenosis and atrial septal defect produce a slight rise, no change, or a small drop during this procedure.[2] It would appear that the change in arterial oxygen saturation in Ebstein's anomaly during hyperventilation is unlike that found in the commoner types of cyanotic congenital heart disease.

The outstanding clinical manifestations of Ebstein's anomaly of the tricuspid valve have been reviewed by Engle, Payne, Bruins, and Taussig.[1] These included a delayed and insidious onset of cyanosis, mild dyspnea, easy fatigability,

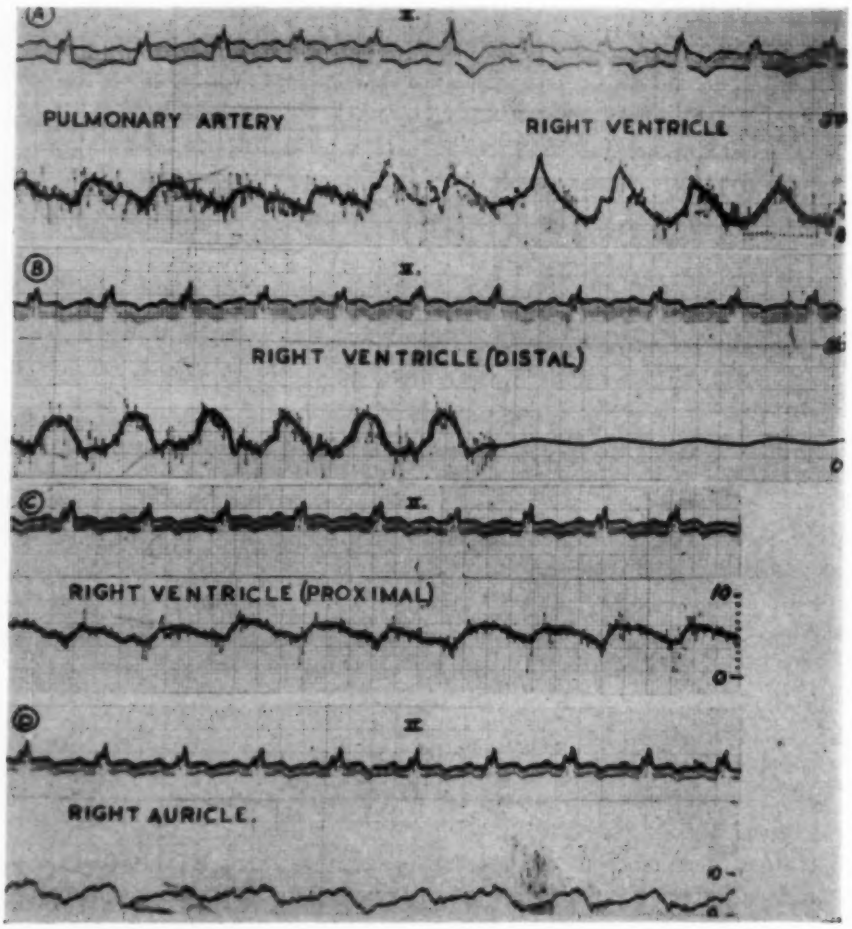

Fig. 7.—Simultaneous electrocardiogram and pressure tracings recorded during cardiac catheterization in Case 1.

A, A continuous pressure tracing recorded while the catheter was withdrawn from the pulmonary artery to the right ventricle.

B, A recording of the pressure in the distal part of the right ventricle. A mean pressure record is shown on the right-hand side of the tracing.

C, A pressure tracing from the proximal part of the right ventricle.

D, A pressure tracing from the right auricle. Numerous artifacts due to free movement of the catheter were present in all the tracings. A line has been drawn through the average of these oscillations.

and infrequent squatting when tired. Physical examination showed an enlarged heart, poor heart sounds, and systolic murmurs. Diastolic murmurs or a gallop rhythm might be heard, and there was no evidence of tricuspid insufficiency. Radiological examination showed an excessive enlargement of the right ventricle with poor pulsations, a concave pulmonary conus region, abnormally clear lung fields, and absent pulsations of the pulmonary arteries. Right bundle branch block and delayed atrioventricular conduction characterized the electrocardiogram. Arterial oxygen unsaturation, a compensatory polycythemia, and a prolonged circulation time occurred.

An insidious onset of cyanosis was found in both the present cases. This occurred at the age of 6 years in one patient and was noted only during cold weather and after exercise in the other.

Systolic and mid-diastolic murmurs were heard in both cases. It is possible that the mid-diastolic murmurs heard to the left of the sternum were due to the smallness of the displaced tricuspid valve, commented on in autopsy reports.[1] Although there was no radiological evidence of mitral stenosis, this could not be excluded. It was of considerable interest that the second heart sound at the base of the heart was considered to be single and pure. The finding of the single second heart sound, together with cyanosis, naturally aroused the suspicion of pulmonic stenosis. This, however, was not found at cardiac catheterization. The most likely explanation of this unsplit second heart sound is the small difference between the diastolic pressure in the pulmonary artery and in the right ventricle.

The resemblance of the radiological findings in these two cases and in those described by Engle and associates[1] is striking. The outstanding feature in the posteroanterior view was enlargement of the heart, predominantly to the left, with a fullness of the cardiac silhouette immediately below a concave pulmonary artery segment. This results in a square-shaped heart. The anterior heart border was flattened against the chest wall in both oblique views, and in the right anterior oblique view there was a prominence of the outflow portion of the right ventricle. The pulmonary arteries were normal or diminished in size.

The pulsations of the heart borders in the posteroanterior view were poor whereas those of the left ventricle in the left anterior oblique view were normal. It is concluded that the right ventricle must form the left heart border in the posteroanterior view, and this was confirmed during cardiac catheterization. That the right ventricle is tremendously enlarged is suggested by these findings and the apposition of the anterior heart borders to the chest wall in the oblique views. The radiological findings would appear to be the result of the dilatation of the congenitally thin right ventricular wall. The two cases described did not show the absent pulmonary artery pulsation or clear lung fields described by Engle and co-workers. The pulmonary artery pulsation was sufficiently marked to contrast with the diminished movement of the right ventricle in Case 1. The venous-arterial shunt and resultant reduction of pulmonary blood were slight. Pulmonary artery pulsation was small in Case 2 where the shunt and resultant reduction of pulmonary blood were marked.

The electrocardiogram was characterized by right bundle branch block. The atrioventricular conduction time has been reported as prolonged,[1] but in our

cases it was found to be at the upper limits of normal. The P waves were prominent in one case, and low voltage characterized all the deflections of the other case.

SUMMARY

The clinical and cardiac catheterization findings in two cases of congenital heart disease have been ascribed to Ebstein's anomaly of the tricuspid valve.

Cardiac catheterization showed a higher systolic and mean pressure in the distal part of the right ventricle than was found in the proximal part. The findings were compatible with the division of the right ventricle into two functionally separate chambers by a displaced tricuspid valve. Evidence for an over-all right-to-left auricular shunt has been discussed.

The clinical picture was that of a delayed onset of cyanosis, systolic and mid-diastolic murmurs, a single second heart sound at the base of the heart, and right bundle branch block in the electrocardiogram. Radiological study showed a markedly enlarged right ventricle sufficiently characteristic to be of diagnostic value.

We are grateful to Dr. J. A. MacFadyen and Dr. A. L. Agranat for referring these patients and to Miss Joanna Whidborne for technical assistance.

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VENTRICULAR TACHYCARDIA FOLLOWING THE ADMINISTRATION OF QUINIDINE

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SEVERAL of the first investigators employing quinidine to correct cardiac arrhythmias noted that it might precipitate ventricular tachycardia.[1-3] Subsequent reports on the treatment of auricular fibrillation with quinidine sulfate mentioned the occurrence of ventricular tachycardia as an occasional complication.[4,5] Greer and Boyer[6] described a single case in detail. Short runs of ectopic ventricular beats which probably represent ventricular tachycardia have also been reported.[1,3,4] It is thus hardly possible to determine the incidence of this complication from the literature. In our series of sixty-five patients with auricular fibrillation treated with quinidine, six developed ventricular tachycardia, suggesting that its occurrence may be more frequent than previously supposed.

CASE REPORTS

CASE 1.—R. M., a 59-year-old white male clerk, was admitted complaining of "skipping heart" and shortness of breath of one year's duration. The heart was enlarged and the rhythm grossly irregular with an apical rate of 112. Blood pressure was 160/80 mm. Hg. No murmurs were heard. There were moist râles at both lung bases. The liver was not enlarged, and there was no edema. The electrocardiogram showed auricular fibrillation with many ectopic ventricular beats from varying foci. Roentgenograms of the chest showed an enlarged heart with mild congestive changes.

On a regime that included bed rest, mercurial diuretics, and salt restriction, he showed satisfactory clinical improvement and lost 6 pounds. Four days after admission, quinidine sulfate was begun by mouth, 0.2 Gm. every two hours for seven doses. The dose was increased 0.1 Gm. daily until he received 0.5 Gm. every two hours for seven doses. The rhythm remained unchanged except for the disappearance of ectopic ventricular beats. He was then digitalized and discharged.

He was readmitted six weeks later in marked congestive heart failure which again responded well. There were occasional ectopic beats. Nine days later he was given quinidine sulfate by mouth 0.4 Gm. every two hours for seven doses and on the following day 0.5 Gm. every two hours for seven doses. The electrocardiogram then showed slight widening of the QRS complex. On the third day he received 0.6 Gm. of quinidine every two hours for four doses, following which he complained of nausea, tinnitus, dizziness, and weakness. An electrocardiogram showed auricular fibrillation with a ventricular rate of 120. The QRS complex had increased from 0.08 to 0.15 second.

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The following morning the patient was found to have a regular rapid rate of 180 unaltered by carotid sinus or ocular pressure. Blood pressure was difficult to obtain. An electrocardiogram revealed ventricular tachycardia (Fig. 1). During the course of ten minutes, 900 mg. of procaine amide were given intravenously with no effect except for further widening of QRS complexes. Two hours later, 15 mg. of morphine sulfate were given intravenously without effect. Three hours later, 20 meq. of potassium chloride in 250 c.c. of plasma were given without effect except for transitory widening of the QRS complex.

The patient now was in marked shock, evidenced by venous distention, unobtainable blood pressure, and cool moist extremities. About fourteen hours after the tachycardia was noted, a left stellate ganglion block was performed using 1 per cent procaine hydrochloride, and shortly thereafter the patient vomited. Twenty minutes later, the rhythm reverted to auricular fibrillation with a ventricular rate of 120 and the rapid disappearance of the signs of shock.

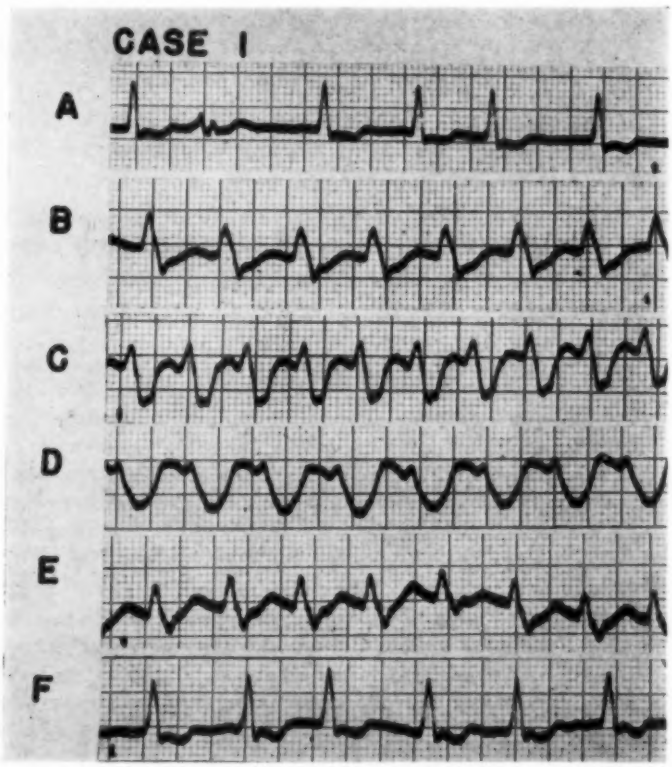

Fig. 1.—Case 1 (Lead II throughout). *A*, Auricular fibrillation before quinidine; *B*, auricular fibrillation with widened QRS complex after third day of quinidine therapy; *C*, ventricular tachycardia following quinidine; *D*, ventricular tachycardia modified by intravenous potassium chloride; *E*, auricular fibrillation with widened QRS complex following stellate block; *F*, auricular fibrillation with normal QRS complex one day following stellate block.

The patient was subsequently admitted on two other occasions in congestive heart failure. On the final day of life he showed spontaneous ventricular tachycardia which failed to respond to intravenous procaine hydrochloride or stellate ganglion block. Permission for autopsy was not obtained.

CASE 2.—W. C., a 57-year-old white male watchman, was admitted because of recurrent dyspnea, orthopnea, numbness and tingling of both legs, and failing memory. He had been told twenty years before that he had heart disease, and he had known of hypertension and auricular fibrillation for an indefinite period of time. For five years he had had exertional dyspnea. Two

episodes of congestive heart failure required hospitalization elsewhere. Physical examination on admission revealed an enlarged heart with a grossly irregular rhythm. The apical rate was 92 and the blood pressure 188/120 mm. Hg. There was a short blowing diastolic murmur at the aortic area. The lungs were clear. There was no edema. The feet were cold, and no pulses could be felt below the femoral arteries. An electrocardiogram showed auricular fibrillation and evidence of an old anteroapical myocardial infarction. The heart was enlarged on x-ray examination, but there was no evidence of pulmonary congestion.

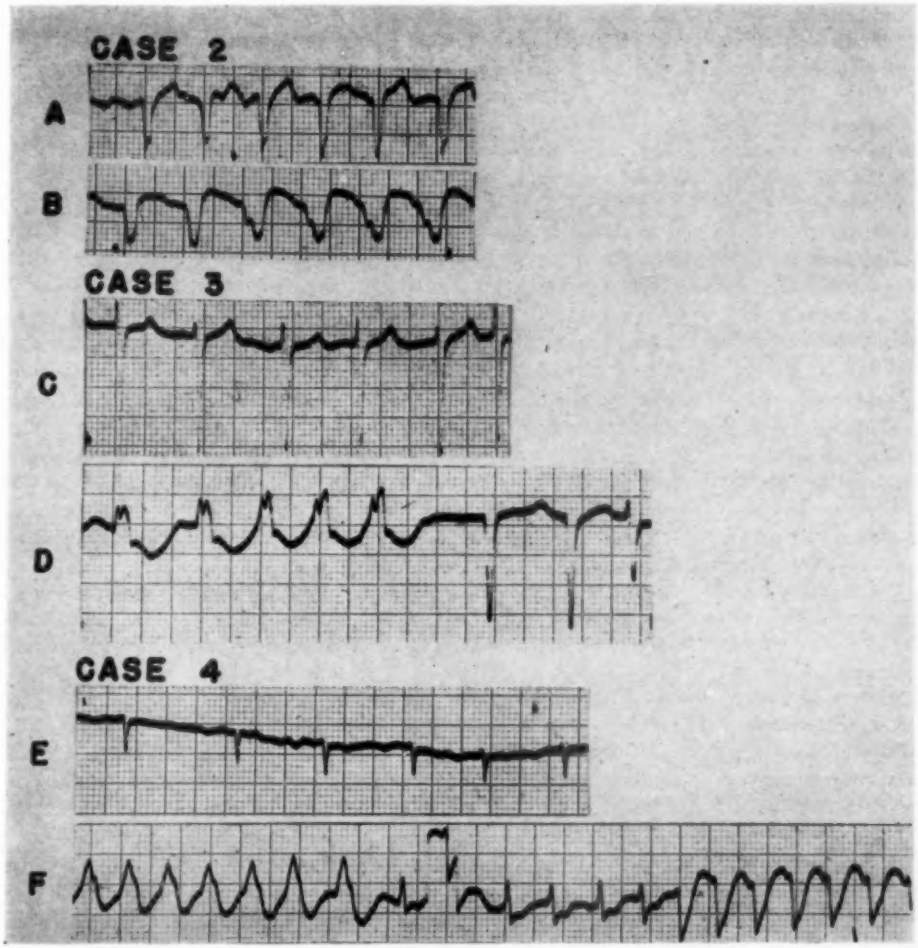

Fig. 2.—Case 2 (Lead II). *A*, Auricular fibrillation before quinidine; *B*, ventricular tachycardia following quinidine. Case 3 (Lead V_2). *C*, Auricular fibrillation before quinidine; *D*, ventricular tachycardia following quinidine. Case 4 (Lead I). *E*, Auricular fibrillation before quinidine; *F*, ventricular tachycardia following quinidine.

Three weeks after admission, a febrile episode occurred associated with chest pain and physical and x-ray findings in the chest which were interpreted as due to pulmonary infarction. The apical rate rose to a level of 130 to 150 despite increased digitalis. An attempt was then made to restore normal sinus rhythm by use of quinidine sulfate.

The patient received 0.3 Gm. of quinidine sulfate by mouth every two hours for five doses and then one dose of 0.4 Gm. That night the electrocardiogram showed short runs of ventricular tachycardia (Fig. 2, *A* and *B*). The next day auricular fibrillation was again present. The

patient continued to fail and died five days later. Post-mortem examination revealed old infarcts of the interventricular septum and left ventricle. There was a mural thrombus in the left auricle and thrombosis of the right femoral vein with multiple infarcts of the lungs.

CASE 3.—G. L., a 64-year-old white unemployed man, was admitted because of shortness of breath of one week's duration. Twenty years previously, cardiac irregularity had been noted. Fifteen years before, thyroidectomy had been performed. During the past ten years he had had numerous hospital admissions for congestive failure, pulmonary emphysema, and fibrosis. Examination revealed a markedly enlarged heart with a grossly irregular rhythm. The apical rate was 100, and the blood pressure was 145/80 mm. Hg. He was severely dyspneic. There was marked emphysema with many rhonchi but no râles. Pitting edema to mid-thighs was present. The electrocardiogram showed auricular fibrillation with many ectopic ventricular beats from varying foci. X-ray examination showed enlargement of the heart but no congestive changes.

Because of the numerous ectopic ventricular beats, digitalis intoxication was considered, and the drug was omitted for five days without effect. A maintenance dose was then resumed. On a regime that included bronchodilators, mercurial diuretics, and a low-salt diet, he showed clinical improvement.

One month after admission quinidine sulfate was begun, 0.2 Gm. by mouth every two hours for seven doses the first day, 0.3 Gm. every two hours for seven doses the second day, and 0.4 Gm. every two hours for seven doses the third day. On the fourth day, following a single dose of 0.5 Gm., an electrocardiogram revealed short runs of ventricular tachycardia ((Fig. 2, *C* and *D*). The quinidine was discontinued, and the patient was subsequently discharged still showing auricular fibrillation.

CASE 4.—J. M., a 57-year-old white male truck driver, entered the hospital because of herpes zoster ophthalmica. Eighteen months previously irregular heart action had been noted. At the time of admission there was moderately severe herpes zoster in the distribution of the ophthalmic branch of the left fifth cranial nerve. The thyroid was firm and uniformly enlarged to twice normal size. The heart was normal in size with no murmurs. The rhythm was grossly irregular with an apical rate of 140. Blood pressure was 148/90 mm. Hg. There were no evidences of congestive failure.

The electrocardiogram showed auricular fibrillation but was otherwise normal. A roentgenogram of the chest was normal. Three basal metabolic determinations varied between +9 and +17. The patient was given 1.2 mg. of digitoxin as an initial dose and subsequently maintained with 0.1 mg. daily.

Sixteen days after admission, quinidine sulfate was begun by mouth, 0.2, 0.4, 0.6, 0.8 Gm. at two-hour intervals. The next day he was given 0.4, 0.6, 0.8 Gm. at two-hour intervals. The third day he was given 0.6 Gm. followed in two hours by 0.8 Gm. Two hours after this last dose, an electrocardiogram showed periods of ventricular tachycardia alternating with auricular fibrillation (Fig. 2, *E* and *F*). The next day auricular fibrillation was again present.

CASE 5.—C. P., a 57-year-old white male electrician, entered the hospital with shortness of breath of three months' duration. Hypertension had been known to be present for four years. Physical examination revealed an enlarged heart and a grossly irregular rhythm with an apical rate of 110 and a blood pressure of 180/120 mm. Hg. There were soft systolic murmurs at the apex and base of the heart and moist râles at both lung bases. The liver was enlarged and tender. Massive peripheral edema extended to the mid-thighs bilaterally. An electrocardiogram showed auricular fibrillation with ectopic ventricular beats from varying foci and left ventricular hypertrophy and strain. On x-ray examination the heart was markedly enlarged, mainly to the left, with congestive changes throughout both lungs, most marked at the right base.

The administration of digitalis and mercurial diuretics, together with a salt-poor diet, led to a loss of 10 pounds in weight, the disappearance of much of the edema, and a fall of the heart rate to 70. Two weeks after admission, an attempt was made to restore normal sinus rhythm. Quinidine sulfate administration was begun with 0.2 Gm. every two hours by mouth for seven doses the first day and 0.3 Gm. every two hours for six doses the second day. The seventh dose was omitted because of nausea and profuse sweating. The ventricular rate was 128 at this time. On the third day, the patient was given 0.4 Gm. every two hours for seven doses without any ill effects. On

the following day, one hour after a single dose of 0.5 Gm., an electrocardiogram showed runs of paroxysmal ventricular tachycardia which became continuous six hours later (Fig. 3, *A*, *B*, and *C*). An intravenous drip of 0.2 per cent procaine hydrochloride was then begun under continuous electrocardiographic observation at the rate of 100 drops per minute for a total dose of 400 mg. in sixty minutes. Within fifteen minutes, runs of conducted beats appeared, and at the end of twenty-five minutes the rhythm reverted to auricular fibrillation with a widened QRS complex. Two hours and fifteen minutes after the cessation of the procaine hydrochloride, normal sinus rhythm appeared and continued uninterrupted during the subsequent four months of observation. The patient underwent surgical repair of an inguinal hernia during this period without complication.

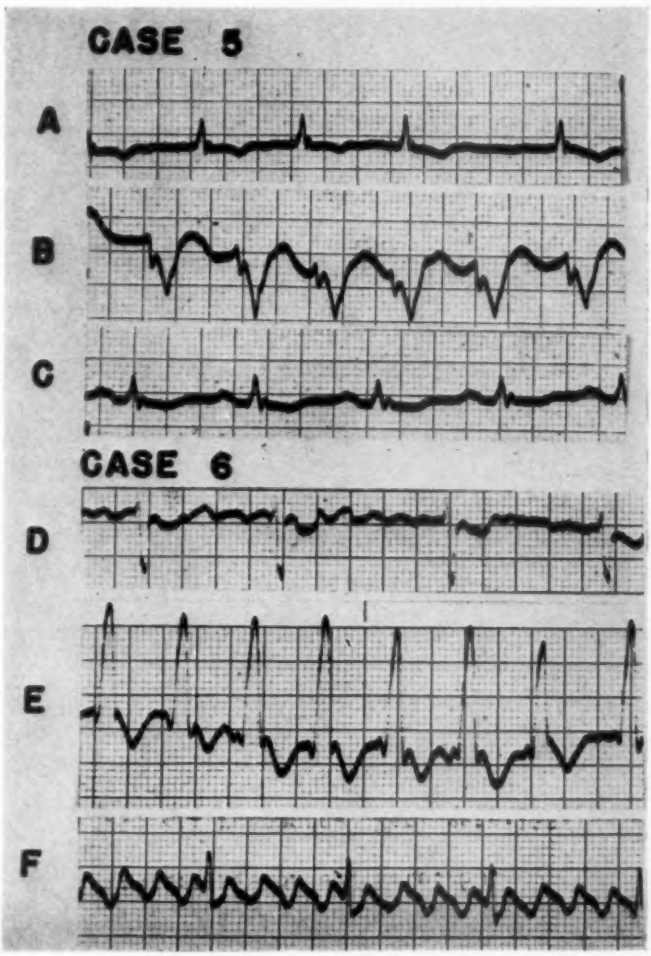

Fig. 3.—Case 5 (Lead II throughout). *A*, Auricular fibrillation before quinidine; *B*, ventricular tachycardia following quinidine; *C*, normal sinus rhythm following intravenous procaine. Case 6. *D* (Lead V_2), Auricular fibrillation before quinidine; *E* (Lead V_2), ventricular tachycardia following quinidine; *F* (Lead II), auricular flutter with varying ventricular response following intravenous procaine hydrochloride.

CASE 6.—J. M., a 28-year-old white male postal clerk, was admitted because of substernal pain of several hours' duration. He had been discharged from the Navy in 1946 because of rheumatic heart disease. For two years he had had dyspnea on exertion. Examination revealed a blood pressure of 112/64 mm. Hg and an enlarged heart, with a systolic and diastolic murmur at

the mitral area. The rhythm was grossly irregular with an apical rate of 70. The chest was clear. The liver was enlarged and tender. He ran a spiking fever to 101° F, complained of left hypochondrium and flank pain, and developed a palpable spleen. Despite ten negative blood cultures, penicillin therapy for bacterial endocarditis was instituted. Auricular fibrillation with a ventricular rate rising to 130 to 150 continued despite digitalis. Accordingly, an attempt to convert to normal sinus rhythm was made. On the twenty-sixth hospital day he was given quinidine lactate 0.2 Gm. intramuscularly every two hours for six doses. He became nauseated and vomited during the night. The electrocardiogram remained unchanged. The following day, he was given 0.3 Gm. of quinidine lactate intramuscularly every two hours for four doses. Forty-five minutes after the last dose, the electrocardiogram showed continuous ventricular tachycardia (Fig. 3, *D*, *E*, and *F*). Seven hours later, 200 c.c. of 0.1 per cent solution of procaine hydrochloride were given intravenously with reversion of rhythm to auricular fibrillation and runs of ventricular tachycardia. The following morning, he showed auricular flutter with 2:1 response. He continued to show auricular flutter with varying ventricular response, at times 1:1, which eventually was controlled by additional digitalis and finally reverted to auricular fibrillation.

DISCUSSION

The accepted criteria for the electrocardiographic diagnosis of ventricular tachycardia cannot be applied with certainty in these cases. The presence of auricular fibrillation precludes the determination of an independent auricular rhythm. The well-recognized quinidine action of delaying intraventricular conduction raises the question whether the observed abnormalities may represent delay in impulse spread rather than origin from an ectopic ventricular focus. Transient bundle branch block as a result of fatigue when a critical rate is reached, as described by Vesell and Kraemer,[7] must also be considered. However, the diagnosis of ventricular tachycardia appears justified in these cases for the following reasons: The QRS complexes differed from those recorded when auricular fibrillation was present and in many instances resembled previously occurring ectopic ventricular beats. The new ectopic rhythm was almost regular, contrary to what would be expected if the fundamental mechanism remained auricular fibrillation with delayed intraventricular conduction. Where the onset of the paroxysm was observed, there was always a premature beat with an abrupt increase in rate. This would not be expected if the sudden change in QRS duration is to be ascribed to delayed intraventricular conduction either as a result of quinidine or the development of bundle branch block.

Although it is a common observation that ventricular ectopic beats and ventricular tachycardia frequently occur with myocardial infarction, there was no clinical or electrocardiographic evidence of acute injury to the myocardium in any of these cases. One patient (Case 2) had evidence of old myocardial infarction at autopsy.

Ventricular extrasystoles occurring singly or in groups are often the precursors of ventricular tachycardia. In Cases 2 and 4 there was neither electrocardiographic nor subjective evidence of ectopic beats. In Cases 1, 3, and 5, which showed ectopic ventricular beats, these were present unchanged and did not occur in pairs or runs in serial electrocardiograms for two weeks to a month prior to quinidine therapy. Ectopic ventricular beats were present prior to quinidine administration in 30 per cent of all the treated cases and in 32 per cent

of seventy patients with auricular fibrillation who were not given quinidine. None of the latter group developed ventricular tachycardia.

There is a divergence of opinion regarding the simultaneous use of quinidine and digitalis.[8,9] All these patients were receiving digitalis, but none had toxic symptoms. The sequence of events in each case strongly incriminates quinidine as the agent which precipitated ventricular tachycardia, but the possibility that the two drugs acted synergistically in this respect cannot be denied.

In the light of currently suggested quinidine dosage schedules, one would not anticipate serious toxic manifestations from such doses as were used in these patients.[10] It is important, however, to recognize that increase in intraventricular conduction time, prolongation of the Q-T interval, and the appearance of frequent ectopic ventricular beats are not necessarily related to excessive dosage and are indications to discontinue quinidine. Close clinical observation and frequent electrocardiograms are required during the administration of quinidine.

Intravenous procaine has for some time been a recognized therapeutic measure in the treatment of ventricular tachycardia. Greer and Boyer were the first to record its use in ventricular tachycardia precipitated by quinidine.[6] Intravenous procaine hydrochloride terminated the ventricular tachycardia in two patients in this series. It is also possible that the procaine used for the stellate block in an additional patient (Case 1) may have been responsible by direct action rather than by the inhibition of sympathetic cardio-accelerator impulses at the ganglion.

Four of the six patients in this series were in congestive heart failure. Askey[11] has stated that even in the presence of congestive failure the liability of sudden death after quinidine is statistically little more than the natural risk of sudden death from the heart disease itself. Nevertheless, it is generally agreed that advanced heart failure is a contraindication to the use of quinidine, barring those exceptional cases where the condition of the patient is progressively deteriorating due to rapid fibrillation which other measures have failed to control.[9,12,13]

SUMMARY

Six in a group of sixty-five patients with auricular fibrillation treated with quinidine developed ventricular tachycardia, suggesting that this toxic arrhythmia may be a more common result of quinidine administration than generally believed.

The occurrence of this arrhythmia was not necessarily associated with excessive doses of the drug. Its frequency emphasizes the need for close clinical and electrocardiographic observation during the use of quinidine.

Intravenous procaine hydrochloride proved useful in terminating prolonged episodes of ventricular tachycardia in two patients.

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LIGATION OF THE VENA CAVA IN THE TREATMENT OF HEART FAILURE

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AT THE Inter-American Cardiological Congress, held in Chicago, in June, 1948, Cossio and Perianes[1] made the original proposal for the ligation of the inferior vena cava below the renal veins to control the left cardiac failure that no longer responds to medical treatment, including absolute rest in a suitable position, strict low-sodium diet, administration of digitalis, and mercurial diuretics in adequate amounts.

Through investigations performed upon animals and some clinical experience, these same authors (Cossio and Perianes,[2] Vedoya, Perianes, and Cossio[3]) pointed out the blood pressure drop in the right heart cavities (auricle and ventricle) as well as in the veins of the arm, without increase when the legs were raised after this ligation had been carried out. This was accompanied by an immediate and sometimes dramatic relief of the dyspnea and the edema of the lower limbs, in spite of the marked increase in venous pressure. As drawbacks, they mentioned the occasional production of temporary edema in either or both of the lower limbs, which is usually painful, and the respiratory trouble produced by general anesthesia; preference was given to local anesthesia by means of the procedure of Zavaleta and Pataro.[4]

More recently, Cossio and Perretta,[5] drawing on much wider clinical and pathological experience, attributed the disappearance of the edema in the lower limbs upon the ligation of the vena cava to the improved lymphatic drainage of the lower one-half of the body as a consequence of the drop in venous pressure of the upper one-half, a result, in turn, of the improvement of heart sufficiency. On the other hand, they ascribed the appearance of edema in the lower limbs after the ligation to the block of the lymphatic return through mechanical damage or inflammation of the tributary vessels and ganglions.

Since the initial proposal, important personal experiences have been reported by Gonzalez Sabathié and Cames,[6] Terán and Yaconcik,[7] Gaspary, Tuero, and García Turiella[8] and, recently, Bianchi[9] in the Argentine and by Donzelot and D'Allaines[10] and D'Allaines and collaborators[11] in France, amounting in all to twenty-five patients undergoing ligation of the vena cava as treatment for heart failure. These cases have yielded a significant proportion of favorable and even surprising results. Whether these will be lasting remains an open question owing to the brief time that had elapsed since the operations.

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Further experience affords observations that may provide an answer to this question. It includes operations performed as long as two years ago, and they are useful in making a general consideration of the problem.

MATERIAL AND METHOD

There are details of the clinical conditions and early results of ninety patients over the period March, 1948, to March, 1950, who underwent ligation of the inferior vena cava for severe and uncontrollable heart failure. The complete evolution is known of only thirty-four patients who have been or continue to be under direct supervision.

The youngest was 27 years of age with mitral stenosis and pulmonary edema, the oldest 67 years of age with severe heart failure from arterial hypertension and healed myocardial infarction with auricular fibrillation. Thirty-seven were women, and fifty-three were men.

Thirty-five had a rheumatic valvular defect (three mitral stenosis, six aortic stenosis with regurgitation, and twenty-six polyvalvulitis), forty-eight arterial hypertension with or without coronary arteriosclerosis, five syphilitic aortic regurgitation, and two interauricular septal defects. Fifty-eight had sinus rhythm and thirty-two auricular fibrillation. All had severe heart failure: of the left side with or without pulmonary edema thirty-one, congestive heart failure fifty-nine, but with edema of the legs twenty-five and with ascites or hydrothorax five.

The first two patients and others shortly afterward, twelve in total, were operated on with general or spinal anesthesia, all the rest, i.e., seventy-eight, with anesthesia by local infiltration, some via the lumbar route, the majority via the abdominal retroperitoneal route, according to the technique of Finochietto and Pataro.[12] Only in the first fifteen cases was postoperative anticoagulant therapy administered.

EARLY RESULTS

Of the first twenty patients, five died in the postoperative period ranging from twelve hours to seven days, i.e., a 25 per cent surgical mortality, four from peripheral circulatory failure (three with anuria from nephrosis of the inferior nephron and one with coronary thrombosis) and the fifth from abrupt accentuation of the pre-existing heart failure.

On the other hand, of the last seventy patients only four died in the same lapse of time, i.e., the surgical mortality was 6 per cent. Of the four two died in collapse and anuria, one with collapse and severe pains in the legs, and the fourth from rapid aggravation of the heart failure.

The seven patients dying of collapse were patients with severe arterial hypertension, two in a malignant phase but without renal failure, whereas of the two who died of exacerbation of heart failure, only one had arterial hypertension and the other rheumatic polyvalvulitis.

The remaining eighty-one patients bore the operation without particular distress, except for one with a large hematoma which suppurated several months

later and was the cause of death. Eight required transfusions for collapse, and eighteen had transitory edema in the lower limbs through lymphatic block.

The early results of ligation of the vena cava in these eighty-one patients were as follows: There was no appreciable improvement in eighteen (eleven rheumatic heart disease, six arterial hypertension, one congenital heart disease), i.e., 20 per cent of the total. On the other hand, there was an appreciable, and sometimes even spectacular, improvement in the other sixty-three patients (thirty-four arterial hypertension, twenty-three rheumatic heart disease, five cardioaortic syphilis, one congenital heart disease), i.e., 70 per cent of the total.

By "no appreciable improvement," i.e., lack of success of the operation, we mean the persistence of the same degree of dyspnea and pulmonary congestion and liver congestion and edema, when present.

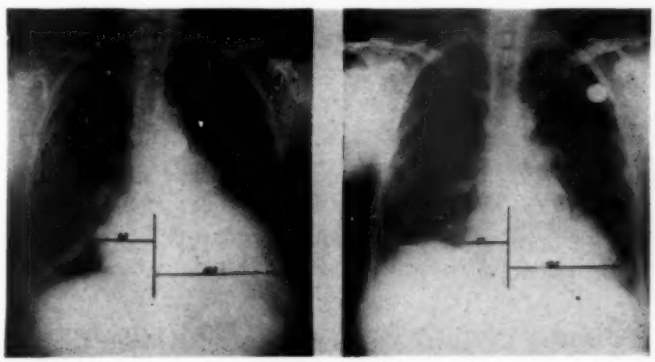

Fig. 1.—Teleradiogram showing the reduction of the enlargement of the heart and of the pulmonary congestion immediately after ligation of the inferior vena cava in one patient with hypertensive heart failure.

By "appreciable improvement," i.e., success of the operation, it is understood that the orthopnea disappeared, and the pulmonary congestion diminished as well as the liver congestion, the edema, and the ascites, if there had been any. All of this generally coincided with a reduction in size of the heart, which was sometimes quite impressive (Fig. 1), the disappearance of gallop rhythm and pulsus alternans, fall of venous pressure in the upper limbs without increase when the lower limbs were raised, reduction of the elbow-lung and elbow-tongue circulation times, increase of vital capacity, and lowering of blood pressure in the right heart.

LATER RESULTS

The improvement immediately achieved upon the ligation of the vena cava proved lasting and persisted for months in fifty-one of the sixty-three patients, i.e., 56.7 per cent of the total.

Of the twelve patients who relapsed into the same state of heart failure as before the operation, seven had rheumatic heart disease and recurrent edema of the lung, two syphilitic aortic regurgitation, and three hypertensive heart disease.

On the other hand, those who continued in a good condition (some were able to return to sedentary occupations) were patients with heart disease from arterial

hypertension or rheumatic heart disease. This was especially so if they had previously displayed local phenomena in the legs suggestive of phlebothrombosis (varicose veins, ulcers, edema out of proportion to the heart failure) or recurrent lung symptoms suggestive of pulmonary infarction (paroxysmal dyspnea, hemoptysis, or pulmonary congestion).

This recovery has lasted two years, the maximum observation period, in 40 per cent of our patients who showed early improvement. At present there are eight patients still under observation whose operations took place more than eighteen months ago who are leading pleasant lives; they only complain of dyspnea upon effort and this not intense. Others, for example, the first and second to be operated on, died months after the operation (one twenty-two months), not from heart failure, but from vascular accidents such as coronary or cerebral thrombosis.

The improvement achieved was sustained, provided the patients continued medical treatment for heart failure, though in most cases not so strictly as prior to the operation. As long as the administration of digitalis and the restriction of sodium were kept unchanged or nearly so, the patient's dry weight could be maintained, even when the mercurial diuretics were spaced out and he was allowed greater activity.

Whenever the patients, because they felt better or believed themselves to be cured, neglected or gave up these precautions, the heart failure returned, but it could be controlled again by resuming medical treatment. Particularly instructive in this respect were two patients, both with hypertensive heart disease and left bundle branch block, 12 and 17 months having passed since the operations, who on several occasions felt better and began eating salt, leaving off the mercurial diuretics and omitting adequate doses of digitalis, with the result that the orthopnea and the edema returned each time.

COMMENT

The experience gathered over two years from ninety patients with uncontrollable heart failure in whom the inferior vena cava was ligated in an endeavor to improve the condition has borne out that such a procedure is justified in view of its relative harmlessness and the significant proportion of favorable results achieved, in most cases sufficiently prolonged.

In fact, the initial surgical mortality of 25 per cent was reduced to 6 per cent through the perfecting of the infiltration anesthesia and even the utilization of spinal or general anesthesia in hypersensitive people, and also by greater care in hemostasis, a close watch for collapse, and the elimination of unfavorable conditions, such as arterial hypertension either in the malignant phase or in extremis.

Another factor that seemed to play a part in the decrease of the surgical mortality was the elimination of anticoagulant therapy in the postoperative stage when it was found that the edema that might supervene was not due to a retrograde venous thrombosis, but to a block of the lymphatic return.

As for the early results, many of them have been remarkable. Patients who entered the operating room in a semirecumbent posture left in a perfectly recum-

bent position and in the nights following slept well lying down without needing to resort to morphine. If, at the same time, there was hepatic pain, edema, and even hydrothorax and ascites, the first soon disappeared, and the rest attenuated or vanished.

Along with this the heart rate was slower; the blood pressure fell but later generally rose again; the enlargement of the heart was reduced; the gallop rhythm and pulsus alternans disappeared; the pulmonary fields cleared; the vital capacity increased; and the circulation time and venous pressure in the arms declined. On the other hand, the venous pressure in the legs showed a marked rise.

This satisfactory condition in 50 per cent of the total number of cases has continued for many months, provided that the medical treatment was strictly adhered to, although in most cases no very intense measures were required to keep down the weight, particularly as far as the mercurial diuretics were concerned. Whenever the patients considered themselves well enough to omit treatment, especially if they neglected to limit their ingestion of sodium, they were faced with the return of the dyspnea, the hepatic congestion, and the edema, these last without great modification of venous pressure; this bears witness to the secondary part it plays, so long as a good lymphatic drainage is carried out, and also to the importance of the sodium ion in their genesis.

At first, the early improvement was attributed to the reduction of venous return by reason of the ligature, with the consequent improvement of cardiac capacity.

The further observation that the most lasting and surprising recoveries were made by patients with recurrent paroxysmal dyspnea and hemoptysis, as well as signs in the legs suggestive of phlebothrombosis, induces one to believe that the ligation of the vena cava has a favorable effect upon uncontrollable heart failure not only through the hemodynamic modifications mentioned, but also because it may put an end to a source of microemboli that show no manifest clinical features, but which may prove to be a contributory cause of persisting heart failure.

SUMMARY

Over a period of two years, the author observed in detail ninety cases in which ligation of the inferior vena cava was carried out for uncontrollable heart failure. The surgical mortality was initially 25 per cent; it was soon reduced to 6 per cent.

Early improvement, sometimes most surprising, was observed in 70 per cent of the patients and was maintained for months or even years in 56 per cent, provided medical treatment was continued.

The early improvement is attributed to the reduction of blood return to the heart and the later improvement to the formation of a lake of blood with a slower return in the recumbent position and also to the elimination of the source of microemboli.

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Clinical Reports

TRANSIENT INTRAVENTRICULAR BLOCK IN CARDIAC CONTUSION

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INTRAVENTRICULAR block as a manifestation of cardiac injury in nonpenetrating trauma to the chest is rare. Standard texts of cardiology[1-4] either do not mention it or merely list trauma as a rare cause. In a review of intraventricular block, Rosenman, Pick, and Katz[5] quoted White's text listing trauma as a rare cause and made no further mention of a relationship. Katz's text on electrocardiography[6] states only that "It (bundle branch block, chronic form) may be found in tumors of the heart or following trauma." No specific instance of traumatic intraventricular block is to be found from these sources.

The literature on nonpenetrating cardiac trauma is somewhat more rewarding. Arenberg[7] reviewed 250 cases of thoracic contusion and found evidence of cardiac damage in twenty-eight. One patient (his Case 16), 46 years old, showed permanent intraventricular block "probably resulting from myocardial contusion." Sigler[8] reported forty-two cases of more severe injuries to the torsum with evidence of cardiac injury in thirty-two, or 76 per cent. One of these (his Case 9), 67 years old, showed intraventricular block with minor shifting characteristics, but the author felt that the intraventricular block probably antedated the injury. Warburg[9] showed an electrocardiogram of intraventricular block among reported cases of cardiac trauma; the age of the patient was not given, and the relationship of the block to trauma was tenuous. Tuohy and Boman[10] reported a case of chest trauma followed by angina in a man 70 years old. An electrocardiogram five weeks after injury showed complete atrioventricular block; one ten weeks after injury showed normal sinus rhythm and right bundle branch block. Subsequent tracings showed both atrioventricular and intraventricular block. Sweeney[11] reported a case of bundle branch block in a man 53 years of age where "the train of events strongly suggest a traumatic etiology."

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In no one of these cases is the patient below the age range where arteriosclerotic coronary disease is reasonably frequent. In each the intraventricular block was permanent; the case of Tuohy and Boman alone presents observation of normal ventricular conduction before or after the trauma.

We wish to present a case of transient intraventricular block in a young man following within twenty-four hours upon moderately severe trauma to the anterior chest wall.

CASE REPORT

A 22-year-old, white, male student was thrown from his motorcycle, striking a concrete bridge abutment with the lower anterior chest. He had always been in good health; there was no history of rheumatic fever.

He was admitted to the hospital forty-five minutes following the accident. The skin was cold and moist. Hiccups were present. He complained primarily of pain about the lower sternum and epigastrium. On admission the pulse was 88, full, and regular, the temperature 97.6° F., respirations 16, and the blood pressure 75/60 mm. Hg.

Examination showed a paradoxical movement of the lower sternum with slight depression of the distal three inches underlying an area of swelling and abrasion of the skin. Crepitation was heard over the lower sternum on respiratory movement. There was tenderness here and in the epigastrium. There was impaired resonance over the lower left side of the chest and slight diminution of breath sounds throughout the entire left lung field. There were multiple superficial abrasions and contusions over the lower extremities and the left arm, a contusion about the umbilicus, and a three-inch submental laceration. There was moderate tenderness in the right costovertebral angle. The left border of cardiac dullness was in the mid-clavicular line. Cardiac action was regular and of normal force. Cardiac sounds were clear. The remainder of the physical examination was negative.

The patient was placed in an oxygen tent and given morphine for sedation and relief of pain. In the first five hours he was given 200 c.c. of plasma, 1,000 c.c. of whole blood, and 1,000 c.c. of 5 per cent glucose in water. At the end of this time, the blood pressure had risen to 110/80 mm. Hg; the pulse fell to 64. The skin had become warm and normally moist. He slept without hiccups.

An initial voided urine was of pink tinge and showed numerous red blood cells; albumin was 4 plus. The white blood cell count was 33,400, polymorphonuclears 85 per cent, red blood cells 4.4 million, and the hematocrit 40. A roentgenogram of the chest showed a veiling density of fluid (? blood) over the left diaphragm. A fracture of the sternum was not demonstrated. An electrocardiogram taken approximately twenty hours after the injury showed a right intraventricular block (Fig. 1).

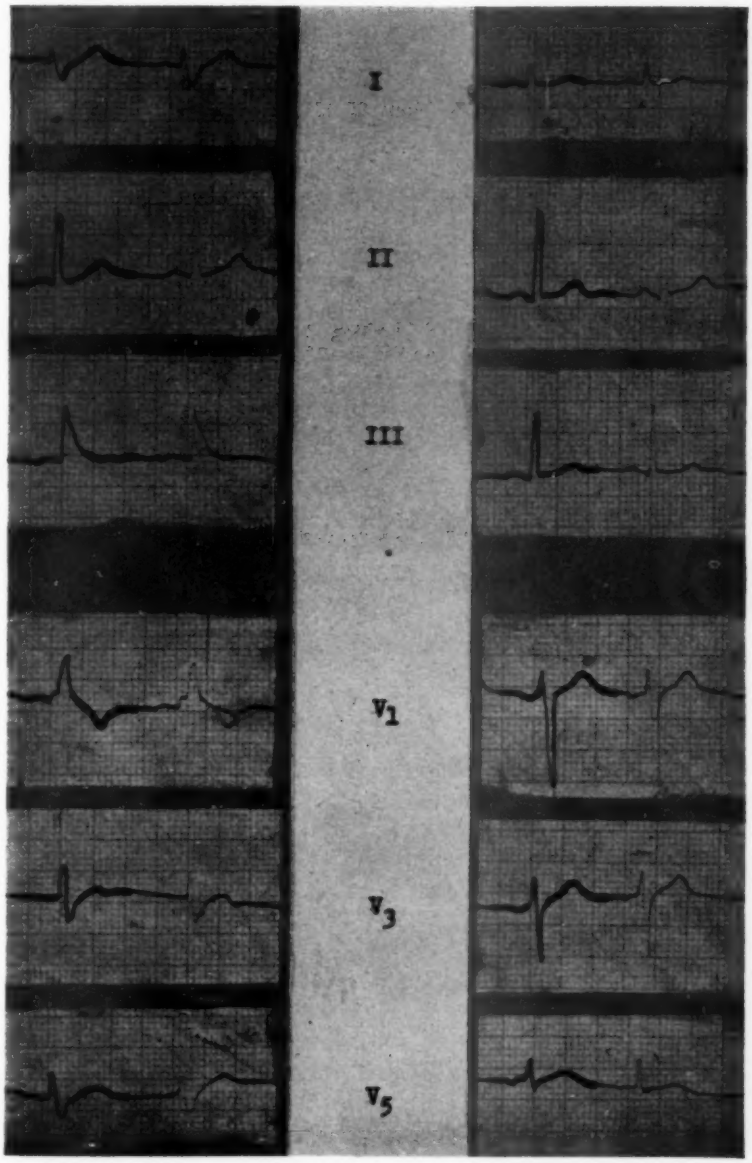
Singultus was intermittent for forty-eight hours. The patient developed a hematoma in the xyphoid area. A mild ileus developed which responded to symptomatic therapy. He ran a low-grade temperature, ranging to 100.8° F. for eight days. The urine cleared, and the white blood cell count fell to 15,700 in five days. The subsequent recovery was uneventful. A chest roentgenogram at the end of eighteen days was negative.

Repeated cardiac examination showed no abnormalities; there was no friction rub. At no time was there pain in the areas of usual cardiac reference. Electrocardiographic tracings at intervals of three days and three months after discharge were normal and without evidence of conduction disturbance (Fig. 1).

DISCUSSION

Warburg, in a comprehensive monograph published in 1938,[12] reviewed the subject of cardiac injury due to nonpenetrating trauma from 1676 to 1937. He and others[7-9,11-15] have continued the review. Cardiac injuries have caused arrhythmias, sudden rupture and death, valvular tears, and pericardial and myo-

cardial damage. Hecht,[16] from similar sources, concluded that myocardial injury from nonpenetrating trauma occurs in three ways: (1) endocardial tear which may penetrate the myocardium, (2) bruise of the myocardium with extravasation of blood and secondary leucocytic infiltration and edema, and (3) direct



A. B.

Fig. 1.—*A*, Right intraventricular block was present twenty hours after chest trauma. There was a widened S_I and S_{V5} and a prominent, widened R_{V1}. The QRS duration was 0.13 second. *B*, Four days after the injury, the QRS duration was 0.08 second. (First complex retouched for photography.)

injury to the coronary arteries with secondary infarction. The relation of trauma to coexistent coronary disease is a vexing one in industrial medicine[7,13,17] but is outside the scope of this report. Moritz and Atkins,[18] in a pathological study in dogs, stated that laceration, interstitial hemorrhage, and tissue disorganization are the changes found in early contusion and should serve to distinguish this type of injury from infarction. This injury, in microscopic section, is well demonstrated in the human heart in a case report by Hodges and Gilmour.[19]

According to these reviews, electrocardiographic evidence of injury has, in the main, been expressed by abnormal ST and T segment changes often resembling infarction. These may occur early or be delayed for days. Minor QRS changes and disturbance of rhythm are not uncommon. Posttraumatic serial tracings are most likely to uncover electrical evidence of damage.

Traumatic auriculoventricular block is less rare than traumatic intraventricular block. Warburg, in his reviews,[9,12] collected ten cases. Coffen, Rush, and Miller[20] reported a case of traumatic complete atrioventricular block observed for eighteen years and added nine complete and three partial atrioventricular block cases, in addition to those of Warburg, from the literature.

Considering the type of injury sustained in cardiac contusion, it is surprising that the conductive system is not more often involved. That it may be more frequently involved is suggested by the animal experiments of Kissane, Fidler, and Koons.[21] They subjected fifteen dogs to varying degrees of trauma by hammer blows delivered to a board placed upon the chest. In the more severly traumatized animals intraventricular block occurred in five with added atrioventricular block in two. These changes tended to be transient unless the insults were repeated. Death occurred in standstill or by arrhythmias. In the whole series pathological evidence of myocardial injury was surprisingly small, consisting mainly of subendocardial or subpericardial hemorrhage. Where demonstrable damage was insufficient to explain arrhythmia or electrocardiographic changes the authors postulated the presence of edema of the myocardium or various parts of the conduction system.

Our case, in the transient nature of the intraventricular block, resembles the findings in the injured dogs of Kissane and associates before trauma was repeated. The youth of the patient and the subsequent demonstration of normal ventricular conduction may make it unique. We believe similar damage could be demonstrated in other instances were serial electrocardiograms taken following body trauma. These observations should be made even though the trauma is not sustained directly to the anterior chest.[8]

CONCLUSION

A case of transient traumatic intraventricular block is presented in a young man 22 years old. A portion of the pertinent literature is discussed.

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COARCTATION OF THE AORTA

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COARCTATION or pressing together of the aorta is usually a diffuse or localized constriction variously located between the left carotid artery and the entrance of the ductus arteriosus. Less commonly, coarctation occurs in other portions of the aorta. Frequently, there are no or slight symptoms, but, when present so as to suggest the diagnosis, they are the result of hypertension in the upper and of sluggish circulation in the lower extremities. While surgery has been used successfully, the selection of proper cases offers difficulties, and the usual signs and symptoms can be misleading. The disparity between the characteristic clinical picture and the anomalous cause for the aortic narrowing, one not correctable by surgery, prompted the reporting of this case.

CASE REPORT

I. S., an 11-year-old girl, had been ill since the age of 5 years with symptoms of tiredness, leg pains, ankle edema, nervousness, severe headaches, fainting spells, nose bleeds, and exertional dyspnea. The voice always was deep and husky. She was well developed and nourished and had a boyish body type, pronounced pulsation in the carotid arteries, a harsh systolic thrill felt over the upper sternum, best over the lower right side of the neck; harsh systolic and blowing diastolic murmurs were heard best in the second left costosternal space, transmitted to the left shoulder, heart apex, and spinoclavicular region. The pulse was greatest in the right wrist, retarded and faint in the abdominal aorta and femoral arteries. The blood pressure in the right arm was 140/80 mm. Hg, left arm 110/80 mm. Hg, and leg 85/70 mm. Hg. An x-ray film of the chest showed the heart and great vessels normal in size and contour with normal ribs.

When the patient was hospitalized, the resting blood pressures were: right arm 140/90 mm. Hg, left arm 115/90 mm. Hg. The femoral pulse was faint and retarded with the pulse not felt in the dorsalis pedis arteries. The dominant complaint was severe headaches. The blood count was hemoglobin 14.7 Gm., red blood cells 5,870,000, and white blood cells 9,000.

Surgical exploration revealed a common arterial trunk arising from the arch of the aorta from which branched the right carotid and subclavian arteries, the left carotid artery, and a small left subclavian artery. The left portion of this common arterial trunk was greatly enlarged and pulsated vigorously. There was no visible constriction of the aorta, but pressure on the aorta at the distal border of the orifice of the large common arterial trunk eliminated the systolic thrill in the aorta and neck. The aortic obstruction seemed to be at the left border of the common arterial trunk and adjacent wall of the aortic arch. Surgical correction was impossible. Preoperative recovery was satisfactory, the severe headaches and blood pressure variation persisting.

A few days after discharge, the patient was readmitted in a semicomatose state, was restless vomiting and tearing at the bed clothes. The right arm and leg were paralyzed, and convulsive movements occurred in the left arm and side of the face. The convulsions became frequent, the temperature rose to 107° F., and she died.

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Autopsy Report.—The pericardial sac was normal, and the right subclavian and right carotid arteries joined to form the right innominate artery which joined the left common carotid artery to form a common trunk arising from the aortic arch. The left subclavian artery was small and arose from the aortic arch, its right half fusing with the left side of the left carotid artery. The aortic ring was thickened, but the valve leaflets were normal. The kidneys were normal, the genital organs small and underdeveloped. The aorta measured 3 cm. in circumference at the arch, at the top of which was the large common orifice of the major neck arteries where the aortic curvature leveled off so that the flow of the ascending aorta faced directly into the large orifice of the common innominate arteries. The distal margin of this orifice was roughened with small fibrinous deposits on the overhanging lip. The brain showed pronounced vascular congestion with no gross hemorrhagic areas or focal changes. The microscope revealed subependymal and subarachnoid hemorrhages.

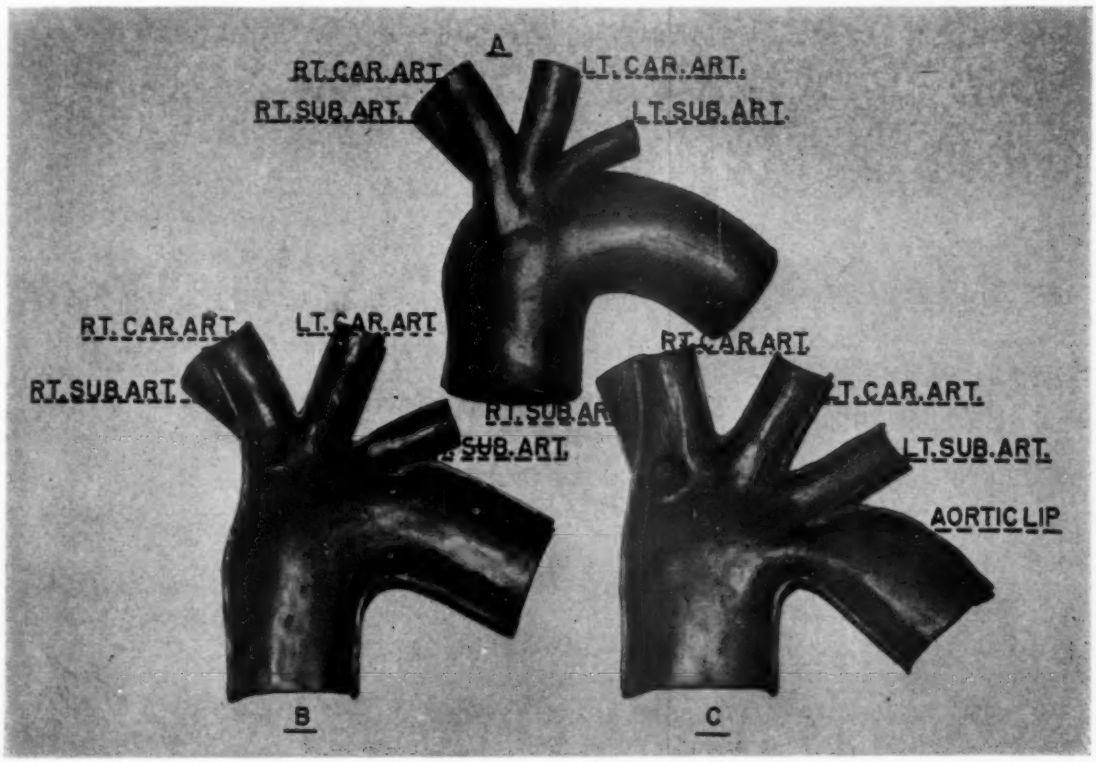

Fig. 1.—Model reproduction of aortic anomaly. *A*, Exterior of anomalous vessels. *B*, Interior of aorta and anomalous neck vessels in late diastole. *C*, The same during aortic systole with anomalous vessels distended and distal lip compressed downward partially occluding the aorta.

COMMENT

This girl had hypertension in the head and upper extremities with sluggish circulation below the diaphragm. The chief symptom of headache was due probably to congestive encephalopathy. Coarctation of the aorta is less common in women, and she had masculine changes and underdeveloped sex organs. Even though the clinical picture was characteristic, there was no organic constriction of the aorta. The clinical picture of aortic coarctation was produced

by the unusual anomalously fused right and left innominate arteries arising from a common orifice in the arch of the aorta (Fig. 1). This orifice was located so as to be in direct line with the upward surge of blood from the ascending aorta. During aortic systole the distention of this common orifice caused a folding downward of the distal upper lip at the point where the left subclavian artery branched from the aortic arch and left border of the left carotid artery. During aortic systole compression of the distal aortic lip produced the systolic murmur and thrill which were abolished by compression during surgical exploration. The clinical syndrome of coarctation, even when pronounced as in this case, is not due always to organic constriction of the aorta, and more extensive diagnostic study is indicated before surgical relief is undertaken.

COARCTATION OF THE AORTA COMPLICATED BY ACUTE BACTERIAL ENDOCARDITIS WITH EMBOLISM OF A CORONARY ARTERY AND SYPHILITIC AORTITIS

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THE purpose of this communication is to report two unusual lesions associated with coarctation of the aorta: embolism of a coronary artery with infarction of the myocardium and syphilitic aortitis. Rheumatic valvulitis and acute bacterial endocarditis, also present in this case, are less rare lesions with coarctation of the aorta.

CASE REPORT

R. V. H., a 29-year-old Negro man, first entered University Hospitals of Cleveland on March 25, 1946, with the complaint of palpitation on exertion. He had had tonsillitis with "rheumatism" at the age of 19 years and also a penile chancre at that age. He had been given sixty "hip and arm shots" at the age of 27 years.

Physical examination showed a blood pressure of 194/92 mm. Hg in both arms with a systolic pressure of 125 mm. Hg in the legs. The left border of cardiac dullness was in the anterior axillary line in the sixth intercostal space. A presystolic thrill with a loud crescendo diastolic and presystolic murmurs at the apex as well as a loud diastolic murmur and a faint systolic murmur in the aortic and pulmonic areas were found.

The hemogram and urinalysis were within normal limits, and the Kline serology test was negative. The chest roentgenogram showed an enlarged heart with diffuse dilatation of the thoracic aorta and questionable nicking of the ribs posteriorly. The electrocardiogram showed evidence of left ventricular hypertrophy while pulse tracings showed marked pulsation in the radial arteries and little pulsation in the femoral arteries (Fig. 1). The vital capacity was 3,200 c.c. (73 per cent of normal). Arm-to-tongue circulation time with magnesium sulfate was 15 seconds, and arm-to-lung circulation time with ether was 10 seconds. The venous pressure was 225 mm. of saline.

On Oct. 28, 1946, the patient re-entered the hospital complaining of upper right quadrant abdominal pain. Three weeks before admission, fever, chills, and cough were noted. He was given one intramuscular injection of penicillin ten days before admission, but the symptoms persisted and exertional dyspnea, orthopnea, and upper right quadrant pain appeared. On admission the temperature was 39.1° C., pulse 120, respirations 25, and blood pressure 190/70 mm. Hg. He was moderately dyspneic and orthopneic, but not cyanotic. The neck veins were distended. There was moderate dullness at the left lung base with increased voice and breath sounds. The heart was unchanged from previous examinations. The abdomen was tense with upper right quadrant spasm, tenderness, and dullness four fingerbreadths below the right costal margin.

The red cell count was normal, and the white cell count was 11,000 with 63 per cent polymorphonuclears. The urine showed 2 plus albumin. Alpha hemolytic streptococci were demonstrated in the blood culture. The venous pressure was 300 mm. saline, the arm-to-tongue (magnesium sulfate) circulation time was 31 seconds, and the arm-to-lung (ether) circulation time was 11 seconds. The chest roentgenogram showed enlargement of the cardiac shadow as compared

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to the previous films as well as passive hyperemia of the lungs. The electrocardiogram on the second hospital day showed evidence of left ventricular hypertrophy and broad P waves.

The patient was given digitoxin with much relief of symptoms and a fall in venous pressure from 300 mm. to 150 mm. of saline. Penicillin, 20,000 units, was given every three hours until the fourth hospital day The temperature fell to normal and remained normal until the eighth hospital day when it rose to 38.3° C. Blood culture on the twelfth day was sterile, but the white cell count was 17,400. Penicillin, 50,000 units every three hours, was again started, but despite this therapy fever persisted. The electrocardiogram on the thirteenth day showed findings suggestive of a recent anterior myocardial infarct. The patient became unresponsive and oliguric. The urine on the day of death showed 3 plus albumin and a few red cells per microscopic field. The patient died on the fourteenth hospital day. He had been given 680,000 units of penicillin during the first four days and 900,000 units during the last two days for a total of 1.58 million units.

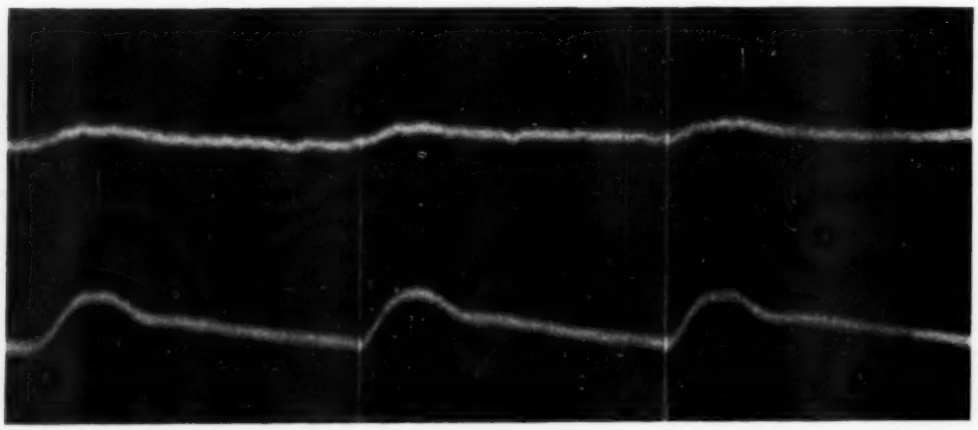

Fig. 1.

The important autopsy diagnoses were (1) coarctation of the aorta with hypertrophy and dilatation of the heart (weight 810 grams); (2) septic embolus of the descending branch of the left coronary artery with recent myocardial infarcts; (3) acute bacterial endocarditis of the aortic valve; (4) rheumatic heart disease with (a) chronic endocarditis of the aortic valve with moderate insufficiency, (b) chronic nondeforming valvulitis of the tricuspid, pulmonic, and mitral valves, and (c) healed endocarditis of the left atrium; (5) saccular aneurysm of the aorta distal to the coarctation with mural thrombus and calcification; (6) dilatation of the aorta and proximal portions of the great arteries proximal to the coarctation; (7) stenosis of the right coronary ostium with tortuosity of the right coronary artery in the proximal portion; (8) recent mural thrombus of the left auricle; (9) septic embolus to the right renal artery with recent infarct of one quarter of the right kidney; (10) bilateral infarcts, small, recent, and old, of the kidneys; (11) healed infarct of the spleen; (12) old infarcts of the cerebrum, small; (13) erosions of the ribs due to dilatation and tortuosity of the intercostal and internal mammary vessels. The post-mortem blood culture was sterile, but alpha hemolytic streptococcus was grown from the vegetations. The post-mortem blood urea nitrogen was 125 mg. per 100 c.c.

The myocardial infarct was at the apex of the left ventricle and measured 3 cm. in its greatest diameter. The aortic valve consisted of three cusps which were deformed by shortening of the cusps and rolling of the margins. There were numerous vegetations. The right coronary ostium measured less than 2 mm. in diameter, so that the left coronary artery supplied most of the myocardium. The coarctation of the aorta was just distal to the ligamentum arteriosum attachment, and the lumen measured 4 mm. in diameter. The ostium of the coarctation opened into a saccular aneurysm with the greatest convexity at the point where the stream of blood emerged from the stenotic lumen and impinged on the aortic wall. The longitudinal diameter of the aneurysm was

3.5 cm., and the wall was hard and 2 mm. thick. The lumen was partially filled by a laminated thrombus (Fig. 2). Microscopic sections showed marked syphilitic aortitis of the arch and descending aorta above the coarctation but not in the wall of the aneurysm or elsewhere below the coarctation.

DISCUSSION

The occurrence of coronary artery disease and syphilitic aortitis is rare in coarctation of the aorta. Reifenstein, Levine, and Gross[1] reviewed 104 cases in the literature between 1928 and 1946, while Abbott[2] collected 200 cases in the literature up to 1928. Reifenstein and associates were able to find only three cases with coronary artery disease, and Abbott made no mention of this complication. Lewis[3] reported the case of a 68-year-old man who had an old anterior myocardial infarct at autopsy. Andreesen[4] reported a 47-year-old man

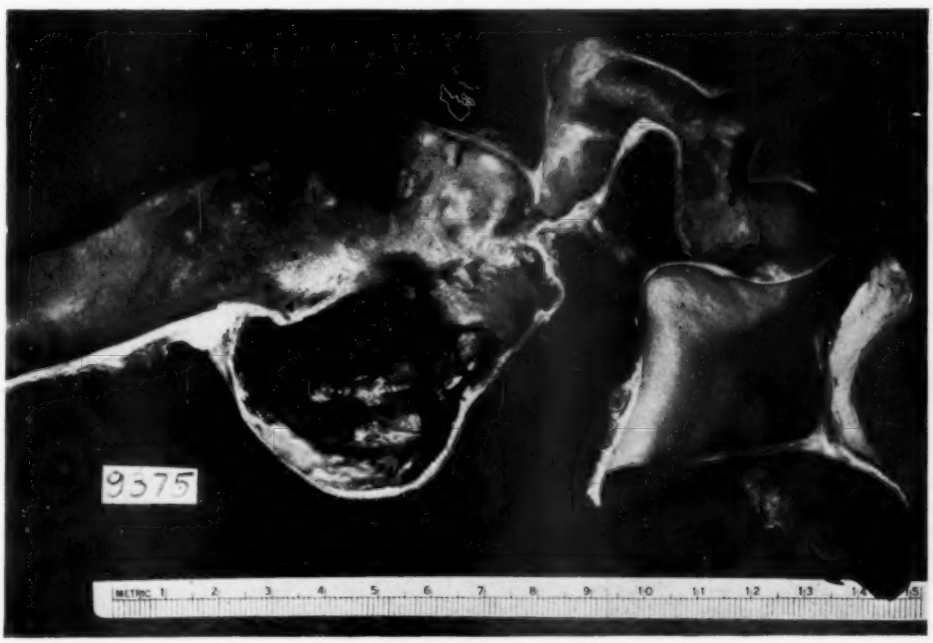

Fig. 2.

who had "myocardial degeneration" at autopsy, but there was no statement as to its cause. Roesler and Kiss[5] reported a 47-year-old man with coronary artery sclerosis but no infarctions of the myocardium. We know of no reports of coronary artery embolism in coarctation of the aorta. Moragues, Bawell, and Schrader[6] reviewed the literature on coronary artery embolism and collected forty-five cases, twenty of which were due to bacterial endocarditis. Gelfman and Levine[7] found that 10 per cent of the patients over the age of 2 years at death who had coarctation of the aorta also had bacterial endocarditis.

Reifenstein and associates[1] found two reports of syphilitic aortitis in cases of coarctation in the literature, while Abbott[2] made no mention of this complication. Von Buday[8] reported a 50-year-old man with a syphilitic aneurysm of the as-

cending aorta. De la Chapelle[9] reported a 33-year-old West Indian man with microscopic evidence of endarteritis of the aorta distal to the coarctation without aneurysm formation at autopsy.

Thus, in this case five separate etiological types of heart disease were found: congenital, rheumatic, syphilitic, bacterial, and coronary. According to White,[10] these etiological types encompass 82.5 per cent of the cases of heart disease.

CONCLUSIONS

1. Two unusual complications, embolus of the left coronary artery with infarction of the myocardium and syphilitic aortitis, are reported in a case of coarctation of the aorta with rheumatic valvulitis and acute bacterial endocarditis of the aortic valve.

2. The combined incidence of these five etiological types of heart disease is 82.5 per cent.

The author wishes to thank Dr. Feil of the Department of Medicine and Dr. Lund of the Department of Pathology for their suggestions in the preparation of this paper.

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CARDIAC INVOLVEMENT IN HODGKIN'S DISEASE

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THE case of cardiovascular involvement by Hodgkin's disease herein reported is unique in our series of sixty-three autopsies on persons dead of Hodgkin's disease. In a review of the literature we found only five case reports[1-5] with similar findings; each reported a mass extending into the right atrium.

CASE REPORT

The patient was a white woman 34 years old. The illness had begun six years previously with generalized aches and pains which persisted and became more severe over the right side of the chest. In 1946, five years after the onset of symptoms, enlarged lymph nodes were noted and diagnosed histologically as Hodgkin's disease at another hospital. X-ray treatment caused a remission of symptoms for about two months. In September, 1946, abdominal swelling and edema of the lower extremities set in. Clinical findings consisted of a cough and shortness of breath. enlarged liver, palpable spleen, and enlarged nodes in the neck and axilla. She was given a course of nitrogen mustard, after which there was a remission which lasted until early January, 1947, at which time the fatigue and cough returned. A second course of nitrogen mustard again produced a remission which, however, lasted only until February, 1947, when abdominal swelling, dyspnea, cough, fever, and anorexia became progressively worse.

Paracentesis was performed on Feb. 24, 1947, and 2,400 c.c. of fluid were withdrawn; the fluid reaccumulated quickly. The patient refused further nitrogen mustard therapy and left the first hospital.

On March 24, 1947, she sought admission to St. Vincent's hospital. She appeared to be in the terminal phase of the disease. Lymph nodes were only slightly enlarged, but there was marked edema of the lower extremities, ascites, and pleural effusion. Heart sounds were of poor quality, the rhythm was regular at a rate of 120 per minute, and no murmurs could be heard. A roentgenogram of the chest showed widening of the mediastinum and an infiltration into the right lung root which extended from the hilum into the base. Moderate fever persisted during the six months' stay in the hospital. She received two courses of nitrogen mustard without beneficial effect. To control the persistent ascites and pleural effusion, four paracenteses and two thoracenteses were necessary. Edema of the lower one-half of the body spread gradually. During the last month a visible collateral venous circulation was established over the anterior abdominal wall. It was presumed that this was due to inferior vena cava block from pressure by enlarged lymph nodes. The patient died six months after admission.

Necropsy Findings.—There were 6,000 c.c. of cloudy fluid in the abdomen, 900 c.c. in the right pleural cavity, and 300 c.c. in the pericardial cavity. The right lung was almost entirely replaced by masses of hard, white tissue. A mass of similar nature was found on the posteroinferior surface of the heart fixed to the right auricle, pericardium, and diaphragm (Fig. 1). The right auricle was filled with a mass of hard, white tissue 10 cm. in diameter (Fig. 2) which extended

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through the tricuspid orifice in one direction and to the mouth of the inferior vena cava in the other. Here there was complete occlusion of the orifice. A smaller nodule of similar tissue 1 cm. in diameter was found in the wall of the left auricle at the atrioventricular groove. The superior portion of the pericardium was replaced by a separate mass of similar tissue contiguous to another mass in the hilum of the right lung. Microscopic examination of the various masses revealed the typical pattern of a sarcomatous form of Hodgkin's disease (Fig. 3).

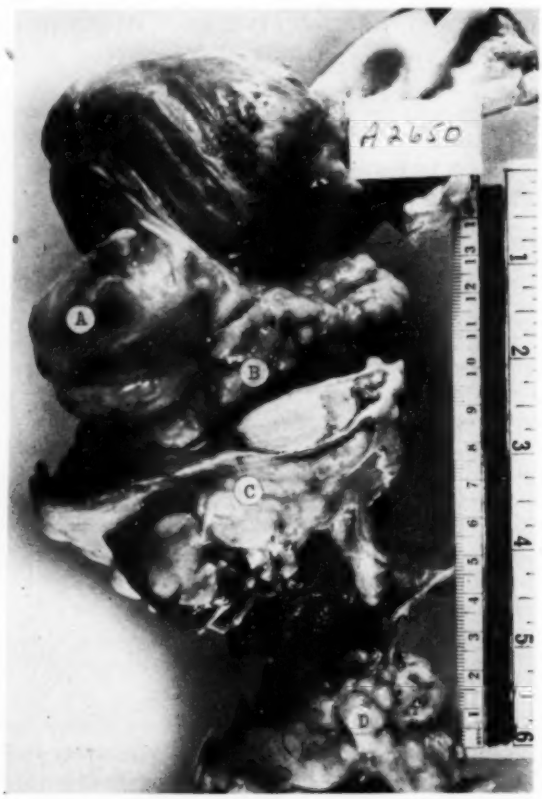


Fig. 1.—Heart, great vessels, and diaphragm en masse. *A*, An irregular, distended auricle filled with tumor. *B*, A tumor mass adherent to the auricle on one side and to the diaphragm on the other. Note (*C*) nodes in the diaphragm and (*D*) retroperitoneal nodes.

Besides these findings, ascites, hydrothorax, and Hodgkin's infiltration of the liver, spleen, breast, and diaphragm were present. There was massive lymph node involvement within the neck, about the trachea and bronchi, in the axillae and groins, about the upper abdominal aorta, and in the lesser omemtum.

The anatomical diagnosis was generalized Hodgkin's disease with unique involvement of the right auricle obstructing the inferior vena cava and tricuspid orifice.

DISCUSSION

Cardiac lesions in Hodgkin's disease are rare, customarily insignificant in extent, and of no particular clinical import. In a series of sixty-three autopsies performed by us on persons dead of Hodgkin's disease, there were only five instances of cardiac involvement by the disease, and in only one of these five in-

stances was the involvement of consequence; in the other four instances the lesions were small and nodular and affected the visceral or parietal pericardium.

Review of the literature confirms our own experience as to the rarity of cardiac lesions in Hodgkin's disease; such lesions are confined to relatively few individual case reports as shown in Table I. It would seem therefore that the myocardium and its appendages constitute a poor soil for the Hodgkin's disease agent.

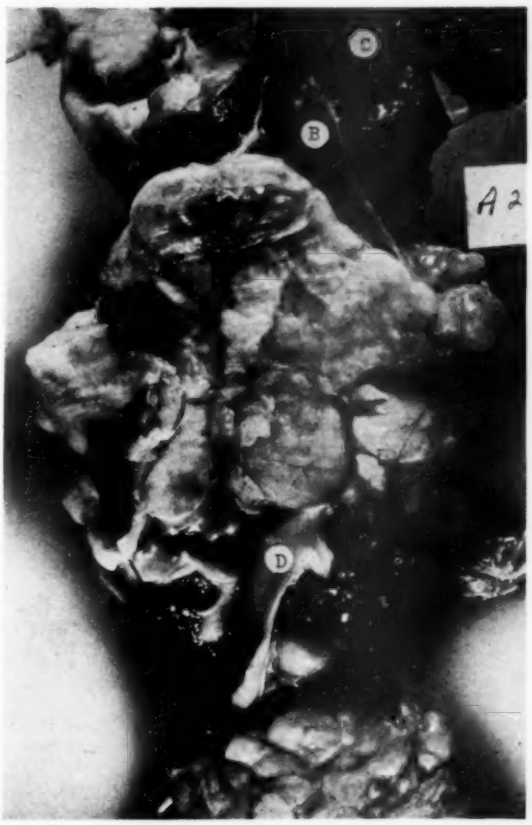
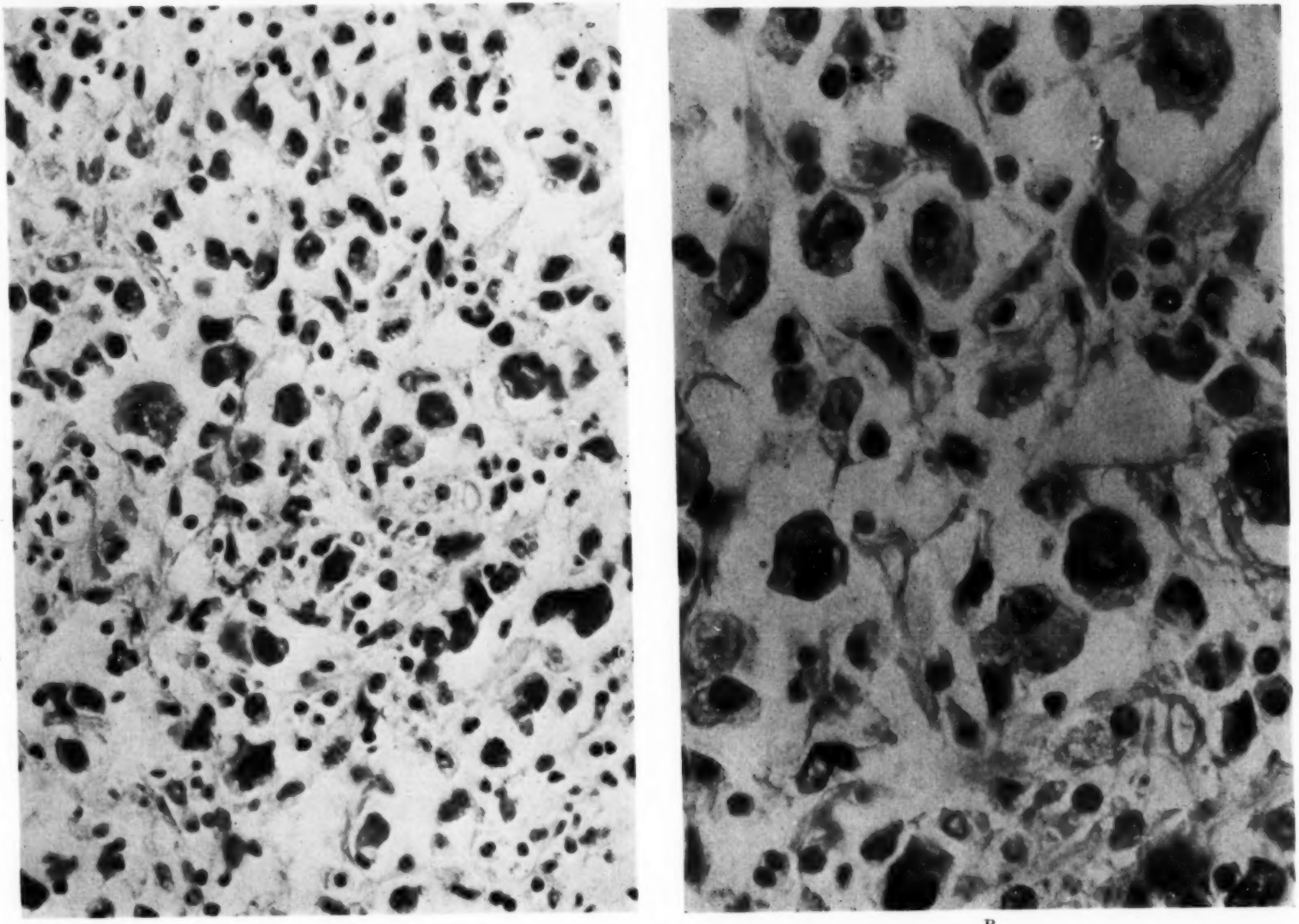


Fig. 2.—Large mass filling the right auricle. *A*, Note how it protrudes through the tricuspid valve (*B*); *C*, right ventricle; *D*, inferior vena cava.

Further study of our autopsy material showed that three other patients had rheumatic involvement of the heart and one had hypertrophy due to hypertension with no Hodgkin's disease present in the heart. In these cases valvular distortion was sufficient to have caused adventitious cardiac sounds and in one instance had been responsible for the congestive heart failure. In the instances where the heart was involved by Hodgkin's disease, heart murmurs and cardiac failure did not occur, except in the case herein described. In this latter instance caval obstruction was complete, and the lungs were practically replaced by tumor, thus making separation of symptoms on the basis of organ involvement impossible.



A. B.

Fig. 3.—Hodgkin's sarcoma. Note hyperplasia of the reticulum and Reed-Sternberg cells present in large numbers. *A*, Photomicrograph, magnification ×100, hematoxylin-eosin stain; *B*, magnification ×400.

TABLE I.

YEAR	AUTHOR	AGE (YEARS), SEX	DURATION OF DISEASE	CARDIAC LESIONS
1902	Reed	9 M	5 yr.	Nodules on pleuropericardial membrane
1915	Yates and Bunting	No clinical data		Visceral pericardium
1929	Terplan and Mittelbach	50 M	5 mo.	Pericardial nodules
1929	Terplan and Mittelbach	22 M	10 mo.	Pericardial nodules
1930	Barone*	29 M	1½ yr.	Mass in right atrium
1934	Rimbaud	69 M	4 mo.	Parietal pericardium
1936	Dalous and Pons	25 M	4 mo.	Infiltration over both ventricles
1936	Krueger and Meyer*	No clinical data		3 cases, pericardial involvement 2 cases, myocardial involvement 1 case, infiltration of right auricle 2 cases, involvement of superior vena cava
1939	Harrell	35 M	6 wk.	Visceral pericardium
1939	Scott and Garvin	No clinical data		Parietal pericardium
1940	Ritvo*	49 F	17 yr.	Mass in right atrium compressing superior vena cava
1941	Catsaras and Patsouri*	33 F		Multiple polypoid masses hanging in right and left ventricles
1941	Garvin*	27 F	10½ yr.	Mediastinal mass involving right atrium
1943	Ayerza and Cernich	38 M		Pericardial nodules with effusion
1948	McCoy	20 M	1½ yr.	Nodules on epicardium
1950	Hagans	26 M		Pericardial effusion

*Findings similar to case described.

Fig. 3.—Hodgkin's sarcoma. Note hyperplasia of the reticulum and Reed-Sternberg cells present in large numbers. A, Photomicrograph, magnification ×100, hematoxylin-eosin stain; B, magnification ×400.

SUMMARY

A case of Hodgkin's disease with massive involvement of heart and lungs is described.

The literature is reviewed and a table made of cases showing the more usual nodular involvement of the pericardium.

The conclusion reached is that the heart is a poor soil for the Hodgkin's disease process.

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Review of Recent Advances

NATURE OF COLLAGEN DISEASES

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THE term "collagen diseases" was introduced by Klemperer, Pollack, and Baehr (1942)[159] to designate a group of maladies characterized morphologically by systemic alterations of the connective tissue. The recognized diseases of this group are rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, generalized scleroderma, dermatomyositis, serum sickness, and periarteritis nodosa.

The collagen diseases in which mucoid degeneration and fibrinoid degeneration and necrosis are prominent features had previously been segregated as "hyperergic" (allergic) diseases (Klinge, 1933).[160] This concept was not accepted because both mucoid degeneration and fibrinoid degeneration and necrosis are commonly found in a great variety of systemic and focal diseases, and there is no evidence of allergy in rheumatoid arthritis, lupus erythematosus disseminatus, generalized scleroderma, or dermatomyositis.[15,155,156] The objections against the view of Klinge have been well expressed by Baehr and Pollack[16] who stated that fibrinoid degeneration "is not a pathological process of sufficient specificity to serve as a reliable common denominator for the classification of disease" and that "acceptance of an allergic basis for these diseases without other supporting evidence serves merely to discourage other avenues of investigation into their essential nature."

In reviewing the collagen diseases, no attempt was made to cover all aspects of these maladies, nor was it undertaken to study all publications which appeared in recent years. However, it was attempted to evaluate critically all knowledge pertaining to the nature of these diseases. The aspects which are considered here are the physiology and pathology of the connective tissue, generally, and the serological, chemical, and morphological alterations of the various collagen diseases, specially. In view of the striking therapeutic effects of ACTH and cortisone in these maladies, certain endocrine aspects are likewise considered.

PHYSIOLOGY OF CONNECTIVE TISSUE

Connective tissue consists of fibroblasts, ground substance, and fibers. Where it borders on other tissues, it may form a basement membrane.

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Ground substance is a plastic material existing apparently in the form of a gel. It is readily demonstrated in vitreous humor, synovia, serosa, and renal medulla; it is difficult to demonstrate in liver, spleen, or adrenals.[8] In young undifferentiated connective tissue ground substance is abundant and continuous; in adult subcutaneous tissue it is less plentiful, being concentrated about the fibers.[28] The gel is greatly hydrated and therefore involved in water binding. This function appears to be related to the hyaluronic acid contained in the ground substance; the sulfated mucopolysaccharides (chondroitin sulfuric acid) and their protein complexes are apparently not involved.[209,214] Normal connective tissue, according to McMaster and Parsons,[204] contains no free fluid, but the electrolytes move through the bound water. In edema and inflammation, however, free fluid accumulates.

The *fibers* of the connective tissue are divided into collagenous, elastic, and reticular fibers. The "fibroglial" fibers, so clearly demonstrated by Wolbach,[338] are probably structural components of the fibroblasts.[49] Electron microscopic studies have shown that connective tissue contains many more fibers than previously suspected.[240] The diameter of the most common fibers measures 500 A. which is beneath visibility with the light microscope. Collagen fibers have long been known to consist of bundles of fine fibrils embedded in an amorphous cement substance. Reticulum fibers differ from collagen fibers in that they stain with silver. As immature collagen fibers and the fibrils of mature collagen fibers likewise stain with silver[160,338] and as no structural differences are found electronmicroscopically,[107] it is believed that they are the same. The elastic fibers, on the other hand, are different in nature; they stain specifically, and they lack fibrils.[49]

The *basement membranes* of connective tissue are composed of collagen and reticulum fibers embedded in a dense, homogeneous, rather plastic material of a gellike consistency. They have been likened to condensation zones at the surface of a gel.[94]

Chemical Aspects.—Ground substance, fibers, and basement membranes have been demonstrated to contain mucopolysaccharides, notably hyaluronic acid and chondroitin sulfuric acid. Hyaluronic acid is a polymer probably of a disaccharide composed of N-acetyl-glucosamine and glucuronic acid. Chondroitin sulfuric acid contains equimolar concentrations of N-acetyl-galactosamine, glucuronic acid, and sulfuric acid.[207-209,211,213,296] The previous contention of Meyer[207,209] that hyaluronic acid differs from chondroitin sulfuric acid in that it is not bound to protein has not been substantiated. It now appears that hyaluronic acid also exists in the form of protein complexes. But whereas chondroitin sulfuric acid-protein complexes are relatively stable, hyaluronic acid-protein complexes dissolve easily.[210,211] Recently, Meyer and Rapport[214] demonstrated the presence in connective tissue of five different mucopolysaccharides; namely (1) hyaluronic acid which is sulfate free, has a specific rotation of -70 to -80 degrees, and is digested at a rapid rate by both testicular and pneumococcal hyaluronidase; (2) hyaluronosulfate which contains sulfate, has a specific rotation of -50 degrees, and is hydrolyzed by both testicular and pneumococcal hyaluronidase; (3) chondroitin sulfate A which has a specific rotation of -30 degrees

and is hydrolyzed by testicular but not by pneumococcal hyaluronidase; (4) chondroitin sulfate B which has the same composition as A, but has a specific rotation of −50 degrees and is resistant to both testicular and pneumococcal hyaluronidase; and (5) chondroitin sulfate C which also has the same composition as A, but has a specific rotation of −20 degrees and is hydrolyzed by testicular hyaluronidase at a rate faster than that of A.

Hyaluronic acid occurs most abundantly in the synovial fluid, vitreous humor, and umbilical cord. Hyaluronosulfate has been found only in the cornea[214] and chondroitin sulfate A only in hyaline cartilage.[214] Chondroitin sulfate B and C are components of the heart valves and tendons.[214] Synovial fluid contains neither chondroitin sulfuric acid nor collagen, while the skin, which is rich in collagen fibers, contains chondroitin sulfate B and hyaluronic acid in about equal concentrations.[214,232,322,323] In myxedema collagen formation is correlated with a shift in concentration from hyaluronic acid to chondroitin sulfuric acid.[322,323] Observations like these seem to show that hyaluronic acid occurs chiefly in the ground substance, while chondroitin sulfuric acid is a component of collagen fibers, cartilage, and other formed elements. As collagen fibers consist of fibrils glued together by cement substance and as the fibrils appear to be protein, it is reasonable to assume that the chondroitin sulfuric acid is a component not of their fibrils, but of their cement substance. This view is in keeping with the failure of Gross[107] to demonstrate mucopolysaccharides within collagen fibrils electron-microscopically.

The chemistry of the basement membranes is not yet clear. There is little doubt that the fibers contained in these membranes consist of collagen. The mucopolysaccharides have not been identified. Sections stained with the McManus-Hotchkiss periodic acid-leucofuchsin procedure[142,202] before and after treatment with proteolytic enzymes (pepsin, trypsin) or depolymerizing enzymes (hyaluronidase, collagenase) seemed to show that they are closely related to hyaluronic acid.[94] In sections stained with the new combined polysaccharide stain developed by Ritter and Oleson,[260] however, basement membranes stain red, whereas ground substance stains blue.[70,81] Similar differences were detected enzymatically. McManus[203] showed that the basement membrane of the renal glomerulus can be removed from sections by pectinase from commercial pectinase or Taka-diastase, while hyaluronic acid or chondroitin sulfuric acid, according to Meyer,[211] is not attacked by this enzyme. Stoughton and Wells[301] found that the basement membrane of skin and blood vessels is distinct from hyaluronic acid in that it is not affected by testicular hyaluronidase. These observations indicate that the mucopolysaccharides contained in basement membranes differ from those in ground substance and collagen fibers.

Formation of Ground Substance and Collagen Fibers.—The relation of fibroblasts, ground substance, and fibers has been ably discussed by Klemperer.[156] It appears that most investigators believe that the mucopolysaccharides are secreted by fibroblasts and that collagen fibers are formed extracellularly, but with the aid of fibroblasts. However, Klemperer[156] has warned that great caution must be exercised in the dynamic interpretation of microscopic pictures. He considers with Kölliker[161] that "as in the secretion of a gland, one part of the

material is derived from external import, but another part from the activity of the cells." He is not convinced that the ground substance is secreted by fibroblasts "because the ground substance might deposit itself independently."

Asboe-Hansen[14] recently postulated that hyaluronic acid may be secreted by mast cells rather than fibroblasts. Good correlation was found between hyaluronic acid content and the number of mast cells in tissues from patients with myxedema. This interpretation is at variance with the demonstration by Jorpes and associates[145-147] and Holmgren and Wilander[140] that the mast-cell content of tissues is well correlated with their heparin content and that the mucopolysaccharides contained in the mast cells are lower sulfuric acids. It is also difficult to reconcile with the high heparin content of mast-cell tumors; one dog tumor studied by Oliver and associates[228] yielded 60.9 Gm. of crude heparin per kilogram with an activity of 492.000 I.U. per kilogram of tissue which is fifty times as much as is found in the liver of dogs. Asboe-Hansen did not determine the heparin content of his tissues. A human scrotum amputated because of elephantiasis (chronic edema) showed numerous mast cells microscopically, and 10 kg. of its tissue yielded 11.1 Gm. of crude heparin, or 1.26 Gm. of purified heparin, with an activity of at least 16.380 I.U. per kilogram of tissue which is almost twice as much as is found in the liver of dogs.[71] The increase in mast cells and heparin in edematous tissue may be a compensatory reaction to prevent clotting of lymph.

The view that ground substance is a secretory product of fibroblasts is in accord with the observation that the appearance of this substance in the monkey's sex skin swelling is associated with marked hypertrophy of fibroblasts.[66] It is in agreement with the finding that the appearance of ground substance in the cock's comb following stimulation by androgens is accompanied by signs of increased metabolic activity in the enlarged fibroblasts such as marked increase in the cytoplasmic ribose nucleic acid.[177] It is strongly supported by the recent demonstration of periodic acid-leucofuchsin positive, apparently secretory, vacuoles within the cytoplasm of fibroblasts during ground substance production.[94,310] The view that the production of collagen fibers depends on both the fibroblasts and the ground substance is in accord with the general experience that tissue cultures of fibroblasts do not produce fibers unless the cells are in good condition[133,298] and in accord with the common observation that the considerable quantities of metachromatic material (ground substance) contained in young connective tissue, or granulation tissue, disappear with the formation of fibers.[34,235,305] Electron microscopic studies of fiber formation in tissue cultures led Porter and Vanamee[240] to postulate that the first fibrils form through longitudinal association of protein macromolecules and that they grow thicker through lateral association of several such fibrils, as well as through progressive deposition of collagen molecules on their surfaces. Meyer[208,209] suggested that the formation of fibers is accomplished through denaturation by the acid mucopolysaccharides of the native soluble collagen protein, which, like the mucopolysaccharides, is secreted by fibroblasts. While the labile hyaluronic acid is removed enzymatically, the more firmly bound chondroitin sulfuric acid is left behind as a film on the surface of fibrils and fibers. These interpretations are in keeping with the early observation of Wolbach[338] that during fiber formation a material staining like collagen first appears as a diffuse deposit about the fibroblasts, and this is followed by differentiation of delicate argyrophil fibrils within the deposited collagen.

It is possible that the lymphocytes may have something to do with collagen formation. Hass and McDonald[133] reported that the largest production of new collagen in tissue cultures was usually associated with the most marked disintegration of lymphocytes and vice versa. This observation is in keeping with the present belief that the lymphocytes function by providing building stones, and also stimuli, for the synthesis of proteins and nucleic acids.[69]

Physiological Regulations.—The production and maintenance of connective tissue depends not only on the activity of fibroblasts and on import from the blood of building stones, but also on regulating principles, such as enzymes, vitamins, and hormones.

The *enzymes* which degrade hyaluronic acid and chondroitin sulfuric acid are known as *hyaluronidases*. They seem to be mixtures of several enzymes, some depolymerizing the long chain molecules, others hydrolyzing the aldobionic acid units formed.[59,11,209,211] Whereas hyaluronic acid occurs in bacteria only in streptococci, hyaluronidases have been found in streptococci, pneumococci, staphylococci, gas bacilli, and other microorganisms. In man, they have been demonstrated in testicles, aqueous humor, and skin. Hyaluronidases from different sources differ immunologically. They also differ enzymatically.[59] The observation of Meyer and associates[212] that chondroitin sulfuric acid is hydrolyzed by testicular hyaluronidase, but not by pneumococcal hyaluronidase, has been confirmed by several investigators.[211] Collagenase, a hyaluronidase produced by *Clostridium welchii* which dissolves mucopolysaccharides of ground substance, basement membranes, and fibers,[94,300] has been found to be distinct.[224] Whether it acts by depolymerizing water-insoluble complex sugars to water-soluble components[94] or by breaking chemical linkages which bind these complex sugars to the polypeptides of collagen has not been determined.[300]

The action of hyaluronidases in vivo is conditioned by the presence of *antihyaluronidases*, such as specific antihyaluronidases, heparin, and the nonspecific hyaluronidase inhibitor. The *specific antihyaluronidases* have long been known.[64] They are antibodies and hence reside in the gamma globulin fraction of the serum. *Heparin*, as is well known, is a mucopolysaccharide and hence may act by competing with the substrate.[4] Isolated polysaccharides of the heparin group are potent hyaluronidase inhibitors.[199,209,264] Alburn[4] found that 1 gamma of heparin neutralizes 1 gamma (250 turbidity reducing units) of purified hyaluronidase. Native heparin-protein complexes may likewise be potent inhibitors.[148] These observations are interesting in connection with the demonstrated participation of heparin in allergic diseases such as anaphylactic shock[63] and serum sickness.[82]

The nature of the *nonspecific hyaluronidase inhibitor* is still obscure. Some investigators[62,112,199] found it to be associated with the serum globulins or, with Cohn's method, with fraction II to III containing alpha 2, beta, and gamma globulins. Others found both the nonspecific hyaluronidase[97,217] and collagenase[300] inhibitor to migrate with the albumin fraction. Good and Glick[102] questioned its linkage to complement as had been suggested previously,[187,312] nor did they find evidence that it is identical with the mucoproteins of the serum.[96] On the contrary, they observed that in lipoid nephrosis the inhibitor was high, whereas the mucoproteins were markedly reduced,[153] and that in rheumatic fever, following ACTH or cortisone administration, the inhibitor returned to normal

usually in ten to fifteen days, whereas the mucoproteins did so only in three to four months.[1] Recent studies suggest that the nonspecific hyaluronidase inhibitor may be heparin. Tissues rich in mast cells and heparin contain significant quantities of inhibitor, whereas other tissues do not.[99] Protamine, which precipitates the polysaccharides of native labile heparin complexes, also precipitates the inhibitor.[287] Peptone shock in rabbits and irradiation sickness in man cause a rise in the serum concentration of both heparin and the inhibitor.[6,98] Their rise in peptone shock can be prevented by intravenous injection of India ink.[98] Snively and Glick[288] found an elevation in the serum concentration of the inhibitor in various liver diseases paralleling the rise in bilirubin, total cholesterol, and other excretory products, while in severe hepatic coma it dropped to low levels. These observations implicate the liver in the formation or elimination of this material. The specific antihyaluronidases are significantly elevated in rheumatic fever, while the nonspecific hyaluronidase inhibitor is frequently increased during the acute stages of most, if not all, collagen diseases. The significance of these rises will be discussed later.

Among the *vitamins* which control the connective tissue, *ascorbic acid* is outstanding. The role of this vitamin in the production and maintenance of connective tissue has been demonstrated and discussed by Wolbach and associates.[338-340] In the absence of vitamin C no collagen is laid down, while the fibroblasts show reduction in phosphatase activity[53] and fatty degeneration.[156,275] Whereas Gersh and Catchpole[94] found an increased amount of apparently poorly polymerized ground substance in scorbutic animals, others[156,235] noted failure in the production of the acid mucopolysaccharides. While Hass and McDonald[133] found no effect of vitamin C deficiency upon fiber formation in tissue cultures, others[144] reported cessation of fiber formation in the absence of ascorbic acid. These contradictory results may be explained by differences in the methods used.[156] They may be quantitative rather than qualitative due to differences in severity of the deficiency.

The mechanism of the effect of ascorbic acid upon the connective tissue is unknown.[254] Wolbach and Bessey[339] stated that the hypothesis that ascorbic acid or a derivate is part of the collagen structure cannot be excluded. Meyer[208] believed that it may be a necessary component of chondroitin sulfuric acid. Reppert and associates[256] have presented evidence to show that it acts by inhibiting hyaluronidase-hyaluronic acid reaction.

It has been demonstrated in recent years that ascorbic acid is closely related to adrenal cortical hormones; the concentration of this acid in the adrenals is higher than in any other tissue.[272] Stress or the administration of ACTH causes prompt release of ascorbic acid from the adrenals,[173,282] a rise of this acid in the blood, and increased urinary excretion.[24] In untreated scurvy the adrenals are greatly enlarged,[171,223,241,248,273] and there is depletion of lipoids.[339] Treatment with cortisone ameliorates the adrenal enlargement and also certain symptoms of the disease.[248,273] The significance of these interrelations is not clear. It has been suggested that ascorbic acid is essential for the synthesis or solubility of adrenal cortical hormones.[24] Seifter[278] has pointed out that the five-membered ring of ascorbic acid with its side chains bears a close resemblance to the five-membered ring (D-ring) of cortisone.

Of the *hormones* which control the connective tissue, *thyrotropic hormone* has been demonstrated to stimulate the production of ground substance and collagen fibers (myxedema).[322] Thyrotropic hormone given to thyroidectomized guinea pigs caused exophthalmus due to a marked increase in the retrobulbar tissues of ground substance associated with an increase in hexosamines both in the tissues and in the blood.[178] On the other hand, ACTH caused softening and decrease in the amount of the firm gelatinous edema of the skin in patients with myxedema.[331]

Similar observations were made with *testosterone*, which was found to stimulate the production of ground substance in the chicken's comb,[38,117,118] and with *estrogens*, which have been shown to cause a similar stimulation in the sex skin of monkeys.[5,66] *Gonadotropins*, on the other hand, appear to induce depolymerization of hyaluronic acid.[36] The latter observation is in keeping with the reported effect of these hormones upon the permeability of the ground substance as measured by the spreading reaction, the permeability being decreased by estrogens[181] and increased by gonadotropins.[294] The mechanisms of these actions are not clear. Duran-Reynals[65] believes that estrogens probably act, directly or through other hormones, by causing synthesis of mucopolysaccharides and increase in their state of hydration, while gonadotropins like hyaluronidase function either by inducing enzymatic liquefaction directly or through stimulation of fibroblasts.

Of particular interest are the effects upon connective tissue of the *desoxy-* and *11-oxy-* and *hydroxycorticosteroids* of the adrenals. It has been demonstrated that desoxycorticosterone acetate, like hyaluronidase, greatly enhances osmosis of semipermeable membranes in vitro and of synovia in vivo, whereas cortisone suppresses it.[279,280] The increase in permeability of capillaries caused by hyaluronidase, as measured by disappearance of Evans blue from the circulation, decrease in serum proteins, and increase in hematocrit,[64,75] is likewise suppressed by cortisone.[26] These observations are in keeping with the finding that anterior pituitary or adrenal cortical extracts markedly decrease spreading in the skin, while adrenalectomy is followed by an opposite reaction.[206,229,326] The significance of these actions is not yet clear. Recent observations[135] seem to support Seifter's view that they are due to action of the steroids upon the hyaluronate substrate rather than upon hyaluronidase. The action of cortisone upon capillary permeability is apparently not a direct effect because it acts only forty-eight hours after injection.[26]

Another effect of desoxycorticosterone acetate upon connective tissue is its stimulating action upon proliferation of fibroblasts and production of collagen fibers, whereas cortisone inhibits experimental wound healing,[238,293] possibly through interfering with the synthesis of chondroitin sulfuric acid.[165] These observations suggest a direct or indirect action of these hormones upon the fibroblasts.

Cortisone and other 11-oxy- and hydroxycorticosteroids may affect the connective tissue also through their catabolic action upon proteins. This has apparently not been demonstrated, but it has been shown that these hormones degrade lymphocytes[332] and plasma cells.[73] The latter observation is of considerable interest in connection with the frequently demonstrated drop in gamma

globulins and antibodies following ACTH or cortisone administration in collagen diseases (see later) and the marked depression of antibody formation following large doses of ACTH and cortisone in rabbits as demonstrated most strikingly by Germuth and associates.[92,93] It appears that this is due in part to the destruction of plasma cells which now appear to be the cellular sources of antibodies and other gamma globulins,[69] although the catabolic effect of these hormones upon proteins may also be involved.

These various observations seem to support the view of Gersh and Catchpole[94] that the connective tissue, including the basement membrane, is in a state of constant flux. It appears that this plasticity is achieved through removal and replacement of ground substance and probably the cement substances, the removal being accomplished through depolymerization and subsequent resorption of water-soluble aggregates by lymph or blood vessels or both and the replacement through direct or indirect action of fibroblasts. The regulators of this turnover include enzymes, vitamins, and hormones, the best known of which are the various hyaluronidases, ascorbic acid, and steroid hormones, notably the sex hormones and the desoxy- and 11-oxy- and hydroxycorticosterones of the adrenals.

PATHOLOGY OF CONNECTIVE TISSUE

The pathological alterations which occur in the connective tissue systemically may be degenerative or proliferative. The degenerative changes which occur in collagen diseases have recently been reviewed by Altshuler and Angevine[7,8] and by Klemperer.[156] They are mucoid degeneration, fibrinoid degeneration and necrosis, and amyloidosis and paramyloidosis. Both the degenerative and proliferative alterations terminate frequently in sclerosis with or without hyalinization.

Mucoid degeneration is characterized by accumulation in the connective tissue of acid mucopolysaccharides, notably hyaluronic acid. It is easily demonstrated in rheumatic fever, rheumatoid arthritis, lupus erythematosus disseminatus, allergic diseases, myxedema, diabetes, prolonged administration of estrogens, androgens, and desoxycorticosterone acetate, and many unspecific injuries. It may occur with or without proliferation of fibroblasts.[8]

The cause of mucoid degeneration is not known. As it occurs in many systemic and focal injuries, it is entirely unspecific. Experimental studies by means of the periodic acid-leucofuchsin procedure of McManus[202] and Hotchkiss[142] have provided evidence that the increase in mucopolysaccharides in inflammation caused by turpentine and in other disorders is associated with depolymerization of the ground substance and probably also of the cement substances.[94] The basement membrane was broadened, thinned, and frayed or altogether indistinguishable during the first two days of the experiments; regeneration with reconstitution of the normal pattern was detectable after three days. The fibroblasts were from the beginning increased in number and contained an increased number of mucopolysaccharide-positive granules in their cytoplasm. This lasted for nine days. Thereafter, the fibroblasts returned to normal. These observations seem to indicate that the accumulation of mucopolysaccharides in

mucoid degeneration is the result of increased activity of fibroblasts. They also suggest that the products of this activity may be in a poor state of polymerization and hence not normal. The term mucoid degeneration may therefore be retained.

Fibrinoid degeneration and necrosis are characterized by deposition in connective tissue of a homogeneous, eosinophilic, highly refractile bandlike material which stains with the Schiff reagent after periodic acid oxidation.[7] This suggests that it contains mucopolysaccharides. It has been stated that it may or may not contain fibrin.[7] Possibly this statement will have to be revised as fibrinoid deposits have been observed to undergo rapid "collagenization"[158] and thereafter are negative for fibrin.[81] Fibrinoid degeneration and necrosis are highly unspecific. They are frequently observed in the various collagen diseases, allergic diseases, infectious diseases, malignant hypertension, Buerger's disease, unspecific inflammations, irradiation damage, mechanical injuries, peptic ulcer, ganglia, hygroma, and certain tumors.[7,156] They are usually associated with, or preceded by, mucoid degeneration.[7]

Fibrinoid degeneration and necrosis have been explained by coagulation of ground substance[158] or by precipitation or inspissation of fibrin or other blood derivates.[41,205] Recent investigations seem to show that the fibrinoid material is not altered collagen, but a precipitate forming in the ground substance,[7] in the cement substance of basement membranes,[81] and apparently also in the cement substance of collagen fibers.[160] The precipitate is possibly one of acid mucopolysaccharides and alkaline protein.[7] The latter may come from the blood plasma (fibrinogen, serum proteins) or from necrotic tissue (collagen, muscles) or both.[7,81] The fibrinoid material therefore is a derivate of both connective tissue and circulating blood.

Amyloidosis and Paramyloidosis.—Amyloidosis is frequently divided into "primary" and "secondary" amyloidosis. Secondary amyloidosis is associated with tuberculosis, osteomyelitis, and other destructive infectious diseases. It is characterized by heavy deposition of amyloid, especially in kidneys, spleen, and liver. Primary amyloidosis is said to occur in the absence of a primary disease. It is characterized by deposition of an amyloid-like material, especially in the connective tissue of heart, skeletal muscles, tongue, gastrointestinal tract, joints, lungs, and skin. Kidneys, spleen, and liver are usually free of amyloid.[74] This classification leaves much to be desired. It is well known that the secondary amyloidosis in plasma-cell myeloma closely resembles primary amyloidosis in every respect. Moreover, Apitz[12] was unable to find any case of primary amyloidosis that was not associated with plasma-cell proliferation. The fact that primary amyloidosis occurs slightly later than plasmacytosis or plasma-cell myeloma suggests that cases of primary amyloidosis are either unrecognized cases of plasma-cell proliferation or cases in which the proliferation subsided (burnt-out cases).

It is recommended to distinguish between amyloidosis and paramyloidosis as suggested by Apitz.[12] This classification is more appropriate because it divides the various cases in two groups with distinct morphological and clinical characteristics.

Amyloidosis and paramyloidosis are characterized morphologically by deposition in the ground substance or basement membranes of a material, staining much the same generally and much like cartilage and mucin.[12] Hass[131] confirmed the finding that amyloid consists chiefly of protein with a mucopolysaccharide content of at least 0.5 to 1.5 per cent. Chemical analysis of the mucopolysaccharides yielded concentrations of nitrogen sulfur, hexosamines, uronic acid, and acetyl closely resembling those of cartilage. Meyer[209] stated that the mucopolysaccharide contained in amyloid differed from others in that it is not digested by hyaluronidase. He suggested that it is closely related to heparin. Hass and associates[132] have shown that amyloid differs from paramyloid in both solubility and affinity for iodine at pH11. The latter observation suggests that amyloid and paramyloid may differ in chemical composition.

The cause of amyloidosis and paramyloidosis is not clear. Genuine amyloidosis is believed to be related to antibody formation.[132,169] This view is in accord with the observation that amyloidosis may be produced experimentally through parenteral injections of foreign proteins.[162,169] As antibodies appear to be gamma globulins formed by plasma cells[69] and as amyloid was observed to develop particularly in animals with low antibody titers, while animals which developed high titers did not acquire amyloidosis,[169] it appears that genuine amyloidosis may be due to faulty production of protein by plasma cells.

It may well be that paramyloidosis also is due to the production of a pathological protein by abnormal plasma cells. This was suggested by Apitz[12] who emphasized the relation of paramyloidosis to proliferation of plasma cells. This is obvious in cases of plasmacytosis and plasma-cell myeloma; it is highly probable in other cases.[12] This view is not at variance with the absence of hyperglobulinemia in most cases of "primary" amyloidosis,[21,74] for low instead of high antibody titers were found in experimental animals which developed amyloidosis.[169] Nor is it at variance with the absence of plasma-cell proliferation at autopsy, if this should occur, for the proliferation may have ceased, while the amyloid, on account of its poor solubility, may have been left behind.

It thus appears that amyloid and paramyloid, like fibrinoid, are precipitates of protein with mucopolysaccharides. They differ from fibrinoid by differences in the proteins involved. While in fibrinoid degeneration and necrosis the protein may come from the fibrinogen of the plasma or collagen of the connective tissue, in amyloidosis it appears to be normal or abnormal globulin formed by normal, or more likely abnormal, plasma cells. The question of whether or not the mucopolysaccharides differ also requires further investigation.

Proliferation of Connective Tissue Cells.—This reaction of the mesenchyme is a common sequel of degeneration and necrosis of both connective tissue and parenchyme (granulation tissue). The ultimate outcome of this secondary proliferation is sclerosis with or without hyalinization (scar formation).

Primary proliferation of connective tissue cells may be observed in myxedema and related conditions where it may lead to edema-sclerosis. More severe degrees occur in generalized scleroderma and probably in other collagen diseases. Marked primary proliferation is a characteristic feature of subacute allergic re-

actions (granulomas). It appears to be preceded by, or associated with, an increased production of ground substance.

The cells involved in primary proliferation may be chiefly fibroblasts or their undifferentiated predecessors, but often they are associated with varying numbers of lymphocytes, plasma cells, and others. Lymphocytes predominate in the lesions of rheumatoid arthritis; plasma cells are most abundant in allergic lesions. Macrophages may likewise be present; they are prominent in the presence of fatty materials.

Allergic proliferations are usually located in the intima or adventitia of blood vessels, in endocardium and myocardium, around nerves and elsewhere. In the arteries they are usually associated with peculiar swelling of the musculature (Verguellung). In the myocardium and in skeletal muscles they may be related to degeneration and necrosis of striated muscle fibers.

The cells of allergic proliferations have been studied by many investigators[68] since they were first described by Oeller[225] and Siegmund.[283] The proliferations in and around small blood vessels have been excellently described and illustrated by Goddard.[100] The initial changes, according to Goddard, are either predominantly endothelial or more markedly, or even exclusively, perithelial. The endothelial cells swell, become more basophilic, and multiply. In short time the lumen is crowded with "monocytoid" and eosinophilic cells. The perithelial cells likewise proliferate. Their forms are not clear-cut at the beginning. They resemble atypical "histiocytes," "monocytoid cells," or "original mesenchymal forms." Later these cells undergo fibroblastic metamorphosis with or without fiber formation. Plasma cells are more frequently seen at the periphery of active granulomas, especially when the nodules fuse or congregate, in granulomas induced by repeated injections of antigen at long intervals, in pericapillary mantlings, and occasionally as small plasmacytic granulomas. Mucoid degeneration is also observed, but fibrinoid degeneration is not conspicuous. The ultimate outcome of the granulomas is partial or entire sclerosis.

Goddard[100] spoke of "reticuloendothelial cells" though he meant "primitive mesenchymal cells, endothelial and perithelial cells, and histiocytes and monocytes." Others spoke merely of mesenchymal cells including plasma cells.[68] As these cells did not phagocytose and many turned later into fibroblasts, macrophages, and plasma cells,[100] it appears that they were not reticuloendothelial cells, but reticulum cells (undifferentiated mesenchymal cells). This interpretation is in keeping with their microscopic appearance.

Sclerosis with or without hyalinosis appears to be the ultimate outcome of proliferation of fibroblasts. It is frequently found in scars, sclerotic arterioles, and regressing uterine blood vessels. It is commonly seen in collagen diseases of long duration, as in generalized scleroderma. Sclerosis is characterized by the presence of many collagen fibers associated with paucity or absence of fibroblasts or other cells. We speak of hyalinosis if the fibers form thick homogeneous bands of a refractile unabsorbable material. The formation of sclerosis is not understood. It appears that it is a local change rather than the result of a generalized metabolic disorder.

PATHOLOGICAL PHYSIOLOGY AND MORPHOLOGY OF THE COLLAGEN DISEASES

Rheumatic Fever

Rheumatic fever is an acute disease of varying intensity and duration with a decided tendency to recur. The patient may recover, or he may die during the first acute phase of the disease, or during a relapse, or as a result of intercurrent diseases or valvular insufficiency long after the acute process has subsided. The first attack occurs most often in children between 5 and 10 years of age.

The etiology of rheumatic fever has been ably reviewed by Waksman.[319] It appears that rheumatic fever is either directly or indirectly caused by, or its cause is associated with, group A hemolytic streptococci. The evidence for this concept is epidemiological, clinical, and serological. The occurrence of rheumatic fever in the wake of scarlet fever is well established. During the last wars associated epidemics of hemolytic streptococcal infections and rheumatic fever were repeatedly observed. It has recently been demonstrated that the incidence of streptococcal infections and subsequent rheumatic fever may be reduced by prophylactic usage of sulfonamide compounds or penicillin.[139]

The serological evidence is equally convincing. The sera from patients with rheumatic fever contain significant concentrations of antibodies to "secretory" products of group A hemolytic streptococci. High titers of antistreptokinase (antifibrinolysin) and antistreptolysin O (antihemolysin) have often been observed.[122] Their maximum concentration was found after the fourth week of the disease[213,269] which is the time when Aschoff bodies are fully developed. High titers of antistreptohyaluronidase have been demonstrated by several investigators.[88-90, 121,123,242-244] The mean titer in fifteen patients with acute rheumatic fever of less than three weeks' duration was over 20.000; in eighty-three acute cases of more than three weeks' duration and in thirty-one subsiding cases, it was 6.000 to 8.000; in 102 chronic or inactive cases it was 2.000 to 3.000. The mean titer of ninety-five healthy individuals was 1024.[242] Significant titers of antidesoxyribosenuclease have recently been described by McCarty.[198] It is interesting that great independent variations with all possible combinations were observed in the response of antidesoxyribosenuclease, antistreptokinase, and antistreptolysin O,[198] but the rise in antistreptohyaluronidase was found to parallel approximately that in antistreptokinase and antistreptolysin O.[88]

The concentration of complement in patients with rheumatic fever has been found to be decreased during the acute phase, but Fischel and associates[79] found it increased rather than decreased, while Wilson and Lubschez[336] found it essentially normal.

Attempts to detect differences in the immunological patterns of patients with hemolytic streptococcal infections who did or did not develop rheumatic fever have not been successful.[9,219,269] However, it was generally found that patients who developed rheumatic fever had greater and earlier antistreptokinase, antistreptolysin O, antistreptohyaluronidase, and antidesoxyribosenuclease responses than those who remained without complications.[9,104,121,124,198,243,244,253,269] This difference was moderate in the case of most antibodies, but in the case of antistreptohyaluronidase it was of considerable magnitude (480 in acute rheumatic fever as compared with 45 in uncomplicated streptococcal infections).[124] The latter antibody also showed better correlation with changes in activity in rheumatic fever than did the other antibodies, although there was no striking correlation between its titer and the severity of the disease.[124] These various observations may be interpreted to signify a greater responsiveness of potential rheumatic fever patients[124] to group A hemolytic streptococci or their products, possibly on a hereditary basis as suggested by Wilson.[334,335]

It is of considerable interest that all types of group A hemolytic streptococci have been cultivated from the upper respiratory tract of patients with rheumatic fever except types 4 and 22[89,163,269] and that an outbreak of sore throat due to type 4 streptococcus in a home for rheumatic children caused no recrudescences.[163] These two types have long been known to be strong hyaluronidase producers,[51,138] but unlike other group A hemolytic streptococci they lack hyaluronic acid. These observations led Dorfman and associates[61] to implicate the hyaluronic acid of the

streptococci in the pathogenesis of rheumatic fever. They suggested that this acid may elicit an overproduction by the host of hyaluronidase which then, through depolymerization of the mucopolysaccharides, may cause a breakup of the mesenchyme and thus prepare the tissues for the rheumatic lesion.

Meyer,[209] on the other hand, implicated the streptococcal hyaluronidase whose entrance into the body in rheumatic fever is clearly indicated by the demonstrated rise in the serum of antistreptohyaluronidase. This view is supported by the observation of Harris and Harris[121] that hemolytic streptococci present in a community in general are relatively good hemolysin, but poor hyaluronidase producers, while the marked rise in the serum of antistreptohyaluronidase indicates good hyaluronidase production by the streptococci involved in rheumatic fever. Meyer's hypothesis is not at variance with the fact that hyaluronidase is produced not only by group A hemolytic streptococci, but also by a variety of other microorganisms which have never been implicated in the etiology of rheumatic fever, because striking differences in specific antihyaluronidase production have been found, for instance, in streptococcal and pneumococcal infections in man, implying that streptococci are much more effective in introducing hyaluronidase into the host than are pneumococci.[122] Meyer's theory seems to be at variance, however, with the observation that types 4 and 22 have not been cultivated from patients with rheumatic fever, although they are excellent hyaluronidase producers. It is conceivable that these two types are ineffective in introducing hyaluronidase into the host.

The evidence reviewed so far leaves little doubt that group A hemolytic streptococci are involved in the etiology of rheumatic fever. It also implicates their hyaluronic acid or hyaluronidase or both. However, it appears that rheumatic fever is not a simple streptococcal disease like scarlet fever, because usually no bacteria are demonstrable in blood or lesions, and there is a latency period between streptococcal infection and rheumatic fever usually of ten to fourteen days. These and other observations have led to the view that rheumatic fever is an allergic response either to group A hemolytic streptococci or to their products,[160,304,306,327] or that it is due to a virus or unknown agent whose entrance into the body is facilitated by the streptococci.[184, 185,274]

The latter view has not been substantiated. The former, on the other hand, is supported by experimental evidence. Swift[304] has pointed out that it has been demonstrated experimentally that, while type-specific hypoergy or immunity results from infection with a given type of streptococci, hyperergy to heterologous types may be present at the same time, suggesting that rheumatic fever may be brought about by a succession of infections with different types of group A hemolytic streptococci.

Experimental reproduction of rheumatic fever has often been attempted. It has been claimed, notably by Klinge[160] and Rich,[258] that serum sickness and similar foreign protein reactions are essentially the same as rheumatic fever, but this has not been accepted.[15,72,221] However, when Swift's theory was put to the test by successive focal infections of rabbits with different types of group A hemolytic streptococci, some of the animals died with cardiac lesions which, in contrast to those in serum sickness, closely resembled Aschoff bodies. The disease thus produced differed from serum sickness also by absence of periarteritis nodosa and by the presence of large adrenals. The latter observation suggests that adrenal dysfunction may be a factor in this disease.

Pathological Chemistry.—Among the chemical alterations in rheumatic fever, changes in the plasma proteins are outstanding. There is a fall in albumin and a rise in fibrinogen and globulin.[54,179] The hyperglobulinemia is at first mainly one of the alpha, and later of the gamma, globulins;[58,167,179,180,186,270,320] the beta globulins, on the other hand, are found without characteristic change.[58] Fractionation by the low temperature-ethanol procedure of Cohn revealed an increase in the N content of fractions II and III which contain the alpha 2, beta, and especially the gamma globulins and a depression of fraction V containing the albumin; there were no characteristic changes in the lipid values of these fractions.[233] The C-reactive protein which precipitates with the somatic carbohydrate of pneumococci and which was first believed to reside in the serum albumin fraction,[3,197] but was later found to be contained in the alpha 1 globulin fraction,[236] has repeatedly been shown to be elevated in acute rheumatic fever. It was found to be low, even with respect to normal, in convalescent patients and in patients with inactive rheumatic fever.[10,197,200,269]

Wilson and Lubschez[336] recently stated that fibrinogen and gamma globulin are elevated in rheumatic fever only if it is complicated by acute infection. This statement is at variance with their data which show that fibrinogen was elevated on the average about 100 per cent in active rheumatic fever without infection and 20 per cent in quiescent cases. Gamma globulin was elevated on the average 100 per cent in active rheumatic fever with acute infection, 50 per cent in cases without infection, and 15 per cent in quiescent cases.

The mucopolysaccharides and the nonspecific hyaluronidase inhibitor (which may be heparin) are also significantly elevated in rheumatic fever.[1,59,101,103,152] The mucopolysaccharides occur as mucoprotein; they are concentrated particularly in the globulin fraction of the serum[59,112,199] and here especially in the alpha and beta globulin fractions.[32,277,325] Their rise in rheumatic fever is in keeping, therefore, with the elevation of the alpha and gamma globulins. The rise of the nonspecific hyaluronidase inhibitor in rheumatic fever suggests that heparin is also elevated.

The rise in gamma globulin in rheumatic fever is explained by the production of antistreptolysin O,[253] antistreptohyaluronidase,[88,89] and other antibodies which have been demonstrated to be contained in this fraction. The observation that the rise in gamma globulin in rheumatic fever is larger and more prolonged than in uncomplicated streptococcal infections[180] is in keeping with the demonstrated greater antibody response (see the preceding). Dole and associates[58] found a good correlation between antistreptolysin O and gamma globulin; Massell and associates[190] observed that ACTH caused a relatively rapid decrease in the concentration of both antistreptolysin O and gamma globulin if these substances were at a high level at the time of therapy. The failure of Dole and associates[58] to remove the excessive globulin from the serum by absorption with living streptococci does not invalidate the antibody theory. It is conceivable that the streptococci used did not contain or produce sufficient antigen, or that part of the gamma globulin consisted of antibody different from that elicited by these bacteria. The observation of Anderson and associates[9] that penicillin therapy in their cases suppressed the production of antistreptokinase and partly of antistreptolysin O, but not of gamma glubulin, has not been explained.

The rises in fibrinogen, alpha globulins, C-reactive protein, mucopolysaccharides, and nonspecific hyaluronidase inhibitor during the acute phase of rheumatic fever are now believed to be unspecific manifestations due to injury of the mesenchyme. A similar rise of these materials has been found in a variety of acute streptococcal and other infectious diseases, in many physical and chemical injuries, and even in certain cases of malignant tumor (fibrinogen,[117,282] alpha globulin, [39,180] C-reactive protein,[10] mucopolysaccharides,[277] nonspecific hyaluronidase inhibitor[101]). The drop in albumin may be due to deficient protein intake or absorption, disturbance of albumin synthesis in the liver, or loss of albumin through kidneys or into pleural or peritoneal transudates, or to combinations thereof.[320] The morbid significance of these various alterations has not been explored. The rise in fibrinogen may have pathogenetic implications. It may be more than coincidence that fibrinoid degeneration and necrosis, and also thrombosis, are common features of these various diseases.

It is interesting that the administration of ACTH or cortisone in patients with rheumatic fever was found to cause a marked drop in fibrinogen[77,226] and a rapid drop in the nonspecific inhibitor to normal levels usually within ten to fifteen days.[1,60] The mucopolysaccharides, on the other hand, returned to normal levels as a rule only in three to four months. The depressing effect of ACTH and cortisone upon these various substances may be explained in part by their catabolic action upon proteins. In part, it may be due to the demonstrated inhibitory action of cortisone upon the permeability of mesenchymal structures[26,279,280] which may prevent their entrance into the circulation.

The *synovial fluid* in rheumatic fever was found by Bauer and his group to be inflammatory in character.[44] It contained 1.000 to 63.000 (10.000) leucocytes per c.mm., with 8 to 98 (46) per cent polymorphonuclear leucocytes, as compared with normal figures of 13 to 180 (63) leucocytes per c.mm., with 0 to 25 (7) per cent polymorphonuclear leucocytes. The protein concentration was 1.6 to 4.9 (3.5) Gm. per cent, with 0.4 to 1.1 (0.7) Gm. per cent of globulin, as compared with normal figures of 0.23 to 2.13 (1.36) Gm. per cent, with 0.05 Gm. per cent of globulin. The mucopolysaccharide concentration was normal: 0.64 to 1.21 (0.87) Gm. per cent as compared

with 0.55 to 1.1 (0.85) Gm. per cent, but the viscosity was low: 31 to 50 (38) as compared with 51 to 403 (203). The latter observation suggests that the mucopolysaccharides of the synovial fluid are greatly depolymerized in rheumatic fever.

Pathological Morphology.—The gross and microscopic changes in rheumatic fever have been well described by Talalajew[307] and especially by Klinge.[160] The structures which are particularly involved are the heart, the joints and adjacent tissues, the skeletal muscles and their aponeuroses and fasciae, the blood vessels, and certain serosal membranes. The skin and subcutaneous tissue, the pharyngeal area, and the nervous system are also often affected. The lesions are located primarily in the mesenchyme connecting organized structures. In the heart they are found in the connective tissue of endocardium, myocardium, and epicardium; in the joints in the loose mesenchyme of the synovial membrane. In patients who died during the first few weeks of the disease, Talalajew[307] and others[7,160] found an increase in the ground substance as well as fibrinoid degeneration and necrosis. The fibrinoid material appeared first within the cementing substance of the fibrils of the collagen fibers, but later was seen outside the fibers as well.[109,160] These degenerative changes were frequently associated with infiltration by polymorphonuclear leucocytes, macrophages, plasma cells, and lymphocytes, and with accumulation of undifferentiated mesenchymal cells. Aschoff bodies, (i.e., focal enlargement and proliferation, especially of fibroblasts, with cytoplasm staining heavily with pyronin indicating increased ribonucleic acid activity,[160] but without fibrin[109]) were found by Geipel[91] in patients who died during the fifth or sixth week of the disease, by Talalajew[307] at the end of the first month, and by Klinge[160] and Gross and Ehrlich[109] after the first month. This is the time when the serum concentration of antibodies against streptococci is highest. The ultimate fate of both the degenerative and proliferative lesions, as is well known, is scar formation (sclerosis).

Individually considerable differences are found in different organs. Fibrinoid degeneration and necrosis are most prominent in the heart valves, joints, blood vessels, and serosal membranes; proliferative changes are outstanding in myocardium and skeletal muscle. Comparatively large areas of fibrinoid necrosis, surrounded by large mesenchymal cells in radial or palisade arrangement embedded in a loose connective tissue, are found in the subcutaneous tissue, tendon sheaths, and other places (subcutaneous nodules). It has been reported that the latter can be reproduced experimentally by injecting blood or saline solution subcutaneously in 90 per cent of patients with active rheumatic fever,[188,189,220] or by subcutaneous injections of trypsin in 70 per cent of patients convalescing from rheumatic fever,[215] but this has not been confirmed.[100,125]

Whereas Talalajew[307] and Klinge[160] believed that the degenerative and proliferative changes in rheumatic fever were two stages of the same process, proliferation following degeneration, Fahr[76] and Masugi and associates[193] suggested that the two may well occur independent of one another, one individual or structure reacting with degenerative, another with proliferative, manifestations. Recent experiences with serum sickness, namely, that fibrinoid degeneration and necrosis are manifestations of an acute and severe antigen-antibody reaction, while proliferation is an expression of a subacute and less severe Arthus reaction, favor Fahr's view. This would well explain the observation that degenerative changes are found in patients who die early from a severe attack of rheumatic fever, while Aschoff bodies are seen in patients who die later from a less severe involvement. The different organ distribution of the degenerative and proliferative changes may be due to differences in the chemical composition of the ground substance and its formed elements, to differences in permeability and fluid exchange, or to other causes.

Rheumatic fever is the only collagen disease in which the plasma cells have been studied adequately. It has long been known that patients with hyperglobulinemia show increased numbers of plasma cells in their bone marrow.[69] It is also known that patients with scarlet fever develop plasmacytosis in the peripheral blood and that this is more severe in patients who acquire complications.[101] Quantitative studies of bone marrow plasma cells were recently reported by Good and Campbell.[101] While healthy individuals contained an average of 19.8 plasma cells per 5,000 nucleated marrow cells, patients with acute streptococcus pharyngitis 35.1, and convalescent pharyngitis patients 60.0, patients with acute rheumatic fever showed an average of 170.0 plasma cells, convalescent rheumatic fever patients 39.1, and patients with inactive rheumatic fever 27.8. Simultaneous studies of serum gamma globulin in these patients revealed excellent correlation with the number of plasma cells.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic disease with decided tendency to exacerbations. It occurs most often in thin women from the ages of 20 to 40 years. The onset may be acute, but is usually gradual. As the disease is nonfatal, morphological studies have been limited largely to chronic stages.

The cause of rheumatoid arthritis is unknown. The old view that this disease is merely a chronic form of rheumatic fever[160] has not been accepted. Many clinical manifestations, such as fever, leucocytosis, rapid sedimentation rate, lymphadenopathy, splenomegaly, and the changes of the joint fluid, suggest an inflammatory process. There is no evidence, however, that it is infectious.[247]

Rheumatoid arthritis differs from rheumatic fever by the absence of significant antibody titers against "secetory" products of group A hemolytic streptococci. There is no rise in antistreptokinase.[44,57,244] The mean antistreptohyaluronidase titer was 1:512 in twenty active cases of rheumatoid arthritis as compared with 1:1024 in ninety-five healthy individuals.[242,243] Antistreptolysin O was found to be slightly, but consistently, elevated,[57] occasionally during the early stages of the disease,[48,222] or not elevated except in patients with associated upper respiratory infection.[244,247] Complement was elevated rather than depressed.[245,316]

It has long been known that rheumatoid arthritis differs from rheumatic fever also in that, in approximately two-thirds of all patients, the serum strongly agglutinates group A hemolytic streptococci.[37,44,48,247,249] It also agglutinates nonencapsulated pneumococci,[56] suspensions of "nonsensitized" collodion particles,[221] and sheep erythrocytes "sensitized" by rabbit antisheep-cell amboceptor.[20,33,267] The substance or substances which cause these reactions are not known. They are apparently not antibodies against streptococci. Wallis[321] thought that they were possibly related to the high globulin content of the serum; this may be true for the sheep-cell agglutinating substance which has been found to reside in the serum globulin fraction.[267] The agglutination of group A hemolytic streptococci and collodion particles, however, was found to be unrelated to the sheep-cell agglutination. Similarly, Ragan and associates[249] observed that, in contrast to the globulins, the streptococcus agglutination reaction did not materially decrease following ACTH administration.

Rheumatoid arthritis may be a metabolic rather than an infectious disease. This is suggested by the clinical observations that it occurs most often in thin women from the ages of 20 to 40 years, that exacerbations of symptoms are experienced nearly always preceding onset of menstruation, and that remission commonly occurs during pregnancy.[136,234] It is further suggested by the fact that the involvement of the joints is not focal, as in infectious diseases, but fairly symmetrical. The common observation that rheumatoid arthritis may be precipitated by psychological or somatic stress and the beneficial effect upon this disease of ACTH and cortisone demonstrated so dramatically by Hench, Kendall, Slocumb, and Polley (1949)[137] implicate the hypothalamic-pituitary-adrenal cortical axis.[247] This view is supported by chemical and hematological studies. Staub and associates[297] noted a slight rise in the urinary excretion of 11-oxycorticosteroids in fourteen patients with rheumatoid arthritis. Venning and associates[317] found the urinary excretion of the glucocorticosteroids and the total (formaldehydogenic) corticosteroids greatly depressed in chronic cases of rheumatoid arthritis, but they found an elevation rather than a depression in several acute cases. This suggests an overstimulation of the adrenals (stress reaction) during the acute phase of the disease followed by hypocorticism later. The observations of Venning and associates[317] are in accord with those of Robinson[262] who found that patients with rheumatoid arthritis as a group did not show as great an eosinopenia following ACTH administration as did the controls, whereas cortisone intravenously caused a similar response in both groups; they are in keeping also with the rise in free and esterified cholesterol in this disease.[167,249] One patient with rheumatoid arthritis studied by Dobriner and associates[56] showed urinary steroids at the lowest level found in healthy individuals. Pregnanolone excreted normally

was absent, but the patient excreted 17-hydroxypregnanolone which, from its characteristic structure, is a metabolite of an adrenal cortical hormone. As this compound was found quite regularly in adrenal hyperplasia and adrenal tumors, but not in the urine of twenty-eight healthy individuals, Dobriner concluded that this arthritic patient had an adrenal dysfunction. Whether or not other patients have similar disturbances, however, remains to be seen.

Pathological Chemistry.—In rheumatoid arthritis, as in rheumatic fever, changes in the plasma proteins are outstanding. The characteristic drop in albumin and the rise in fibrinogen and globulins first noted by Davis[64] were soon confirmed.[276,309] It was found that the hyperglobulinemia, as in rheumatic fever, is due to a rise in the alpha and gamma globulins, the alpha globulins being elevated during the early course of the disease.[57,167,172,180,186,227,302] Moderate increase in the C-reactive protein early in the disease was also noted.[249,321] A rise in the nonspecific hyaluronidase inhibitor was likewise recorded.[115,286] As in rheumatic fever, both the globulin and nonspecific hyaluronidase inhibitor returned to normal following ACTH administration.[115,249,276]

The rise in fibrinogen, alpha globulins, C-reactive protein, and nonspecific hyaluronidase inhibitor in rheumatoid arthritis obviously has a similar significance to that in rheumatic fever and other infectious or noninfectious maladies. The elevation of the gamma globulins in the absence of demonstrable antibodies, on the other hand, has not been explained. It is true, as we shall see, that the tissues in this disease contain a markedly increased number of plasma cells which are believed to be the cellular sources of gamma globulins. The cause of their increase or the nature of their products, however, is obscure.

The *synovial fluid* in rheumatoid arthritis appears to be greatly increased. Ragan and Meyer[250,251] obtained not uncommonly 50 to 70 c.c. from diseased knee joints as compared with 2 c.c. normally. In the cases studied by Bauer and associates,[44] the fluid resembled that in rheumatic fever in that it contained an average of 14.000 (600 to 66.000) leucocytes, 65 (5 to 96) per cent of which were polymorphonuclear leucocytes. The protein content was greater than in rheumatic fever, 4.9 (3.0 to 8.9) Gm. per cent with a greater amount of globulin, 2.2 (1.2 to 6.8) Gm. per cent. The mucopolysaccharide concentration was slightly depressed, 0.52 (trace to 1.35) Gm. per cent as compared with 0.85 Gm. per cent normally, whereas the viscosity was only 17 (4 to 116) as compared with 38 in rheumatic fever and 203 in normal individuals. Similar observations were reported by Meyer and associates[209,250,251] who found that the joint fluid contained 80 to 270 mg. per cent of hyaluronic acid as compared with 80 to 150 mg. per cent normally. These results are interpreted to mean that the hyaluronic acid of the joint fluid in rheumatoid arthritis is greatly depolymerized.[208,210,247,250,251,265,266] It has been suggested that the increase in total hyaluronic acid and its low state of polymerization indicate a defect in the synthesis of the mucopolysaccharides in this disease.[210,247,250,251] This may well be so, but it is not specific, for similar changes have been found in rheumatic fever and lupus erythematosus disseminatus; histological observations seem to show that both increase in hyaluronic acid and decrease in its state of polymerization are common sequels of a great variety of injuries.[8,94]

Pathological Morphology.—The morphological changes in rheumatoid arthritis have been well described by Rosenberg.[268] The organs most prominently affected are the joints and adjacent structures. Other organs frequently involved are the heart, the skeletal muscles, the nerves, the kidneys, and the skin. The serosal membranes may be affected also. Rosenberg[268] noted "adhesive pleuritis" in 73 per cent of his cases. The blood vessels, on the other hand, are usually not involved.

The natural history of the rheumatoid lesions has not been studied as well as that of the rheumatic fever alterations. This is obviously due to the fact that patients with rheumatoid arthritis rarely die during the early stages of the disease. When available for examination, the lesions are usually characterized by proliferation of mesenchymal cells, such as fibroblasts and the related synovial endothelial cells, and by the presence of plasma cells and follicular accumulations of lymphocytes. Fibrinoid degeneration and necrosis are prominent only in the subcutaneous and perineural nodules; they are inconspicuous elsewhere. The fate of these lesions is sclerosis.

The joint changes in rheumatoid arthritis are characterized by the formation of a pannus, i.e., overgrowth of synovial membrane including both synovial endothelium and underlying stroma.

There are varying numbers of plasma cells, lymphocytes, leucocytes and eosinophils; the lymphocytes often form follicle-like structures, the like of which is said not to occur in other joint diseases.[268]

The cardiac lesions in rheumatoid arthritis have been widely discussed since Klinge.[160] Recently, Baggenstoss and Rosenberg[17-19] have demonstrated fibrinoid degeneration, Aschoff bodies, and other changes resembling those in rheumatic fever in 80 per cent of their cases. These were less severe and not as widespread as in rheumatic fever. Similar observations have been reported by others.[23,241] As other evidence of rheumatic fever was found only in 3.4 per cent of the patients[268] and similar changes were found in 90 per cent of the hearts of patients who died from other diseases,[116] it is believed now that these changes are not specific. In the hearts of two patients Baggenstoss and Rosenberg[19] observed lesions closely resembling subcutaneous nodules. These have not been seen in other diseases.

The changes in the skeletal muscles have likewise been widely discussed since Klinge.[160] They were described as widely disseminated nodules composed of compact accumulations of lymphocytes, a few plasma cells, and occasional eosinophils and epithelioid cells, with a definite increase in collagenous connective tissue between the inflammatory cells.[86] These mesenchymal changes were associated with edema, hydropic degeneration, loss of striation, and other changes of the muscle cells. Steiner and associates[299] thought that these lesions were specific. However, other observers[289] found similar lesions in many diseases including rheumatic fever, lupus erythematosus disseminatus, generalized scleroderma, dermatomyositis, tuberculosis, poliomyelitis, renal infections, and others. Hence, it is now believed that they are as unspecific as the cardiac lesions. However, both the cardiac and skeletal alterations are eloquent evidence of the systemic character of the mesenchymal involvement in rheumatoid arthritis.

The subcutaneous nodules in rheumatoid arthritis are usually described as consisting of a central area of fibrinoid degeneration and necrosis surrounded by a zone of palisading spindle cells, probably fibroblasts, the latter being enveloped by fibrous connective tissue containing lymphoid cells and other elements. Altshuler and Angevine[7] found abundant hyaluronic acid within the necrotic zone, while fibrinoid material was deposited in the peristellate zone of fibroblasts. The subcutaneous nodules in rheumatoid arthritis differ from those in rheumatic fever in various aspects. While in rheumatic fever they may exist for only four to six days, in rheumatoid arthritis they often persist for years. While in rheumatic fever they are usually small and solitary, in rheumatoid arthritis they tend to be large and to form agglomerations. These differences have been looked upon as expressions of two different disease processes.[27,46]

The neural lesions are located in the perineurium. They resemble the subcutaneous nodules in that they show central degeneration and necrosis surrounded by proliferating fibroblasts.[85] This is of interest in view of the genetic relationship of the nervous system and the skin.

The renal lesions in rheumatoid arthritis are characterized by proliferative changes within the glomerular tuft.[18] These have been interpreted as endothelial proliferation.[268] As the glomerular proliferation in serum sickness has recently been demonstrated to be intercapillary rather than endothelial, the endothelial interpretation should possibly be reconsidered.

It is of considerable interest that rheumatoid arthritis is not uncommonly associated with amyloidosis. Unger and associates[315] found this complication in 9 per cent of their cases. The literature on this subject up to 1943 has been reviewed by Trasoff and associates.[313] Lövgren[172] has stated that the chemical composition of amyloid, which is believed to consist of globulins and high molecular sulfuric acids such as chondroitin sulfuric acid, suggests that the amyloidosis in rheumatoid arthritis may be due to a combination of hyperglobulinemia and liberation of chondroitin sulfuric acid through destruction of cartilage.

Lupus Erythematosus Disseminatus

Lupus erythematosus disseminatus (L.E.D.) is an acute or subacute disease usually with a prolonged clinical course terminating fatally in most cases, generally within five years. The disease is characterized by a tendency to remissions and recurrences of variable duration. Ninety-five per cent of the patients,

according to Baehr and Pollack,[16] are women in the second to fourth decades. As death occurs as a rule during a period of exacerbation, acute tissue changes are readily available for study.

The cause of L.E.D. is not known. There is no evidence of infection. The hypersensitivity of patients with L.E.D. to light and other injuries seems to be nonspecific; it is due perhaps to the presence of catalysts. An extraordinary response to antigen was reported in a patient who, following a series of eight blood transfusions, developed a remarkable succession of one familiar and three "new" antibodies in her serum.[35] There is no evidence that the disease is allergic in the sense of an Arthus reaction.[16,155,159]

L.E.D. is characterized by the occurrence of the L.E. phenomenon discovered by Hargraves, Richmond, and Morton (1948),[120] namely, the appearance of rosettes of clumped leucocytes and of L.E. cells, i.e., polymorphonuclear leucocytes and macrophages containing homogeneous inclusion bodies. The latter have been identified with the hematoxylin-staining bodies of Gross (1932).[157,166] Polymorphonuclear leucocytes and macrophages with nuclear inclusions resembling L.E. cells have been observed in many tissues. They were found to be present in as many as 96 per cent of all patients with acute L.E.D.[166] Control studies of patients with rheumatic heart disease, rheumatoid arthritis, generalized scleroderma, dermatomyositis, and other diseases were negative with the exception of one case each of multiple myeloma,[119] pernicious anemia in relapse,[29] and primary amyloidosis.[166] Lee and associates[166] have shown that the inclusion bodies in their case, though resembling those of L.E. cells when stained with Jenner-Giemsa, reacted with amyloid stains. They suggested that a similar situation may have existed in Hargraves' case of multiple myeloma, which is often associated with amyloidosis.

The hematoxylin-staining bodies were first observed in cardiac lesions; they were described as "pyknotic and karyorrhectic nuclear masses" staining purple with hematoxylin.[108] Klemperer and associates[157] spoke of "clumps and packets of ovoid or spindle-shaped purple-blue structureless bodies" of about the size of cells easily distinguishable from pyknotic or karyolytic nuclei. These bodies stained a brilliant red with Feulgen's reagent, showed strong absorption of ultraviolet rays at 2.537 A., and hence were identified as desoxyribonucleic acid. The bodies could be traced to the nuclei of fibroblasts, macrophages, lymphocytes, and polymorphonuclear leucocytes. Occasionally, they were contained in apparently normal polymorphonuclear leucocytes or macrophages. Bodies of this type were found most frequently in the tissues of heart and kidneys, but they were also found in lymph nodes, spleen, serosal membranes, synovial membrane, skin, vessels, bone marrow, liver, and elsewhere. They were present in thirty-two of thirty-five cases of L.E.D.; they were absent in other diseases except in one case of generalized scleroderma. As photometric studies with methyl green and Feulgen revealed depolymerization of the desoxyribonucleic acid, Klemperer and his associates[157] concluded that they were evidence of a peculiar damage, possibly due to interference with the enzymatic activities within the affected cells.

The L.E. phenomenon is caused, as shown by Hargraves[119] and Haserick and Bortz,[128] by a factor contained in the serum of L.E. patients (L.E. factor). This was present in twenty-three patients who had been, or later were, diagnosed as having L.E.D. It was absent in ninety-five patients with chronic discoid lupus, rheumatoid arthritis, generalized scleroderma, dermatomyositis, periarteritis nodosa, and other diseases.[126] There was no correlation between the serum concentration of the factor and the activity of the disease process,[166] but when the patients went into remission, the factor disappeared.[127,129] The nature of the factor is not yet clear. It has been shown to be contained in the gamma globulin fraction.[29,129] It has also been demonstrated to be independent of complement.[166] As antiserum to the gamma globulin of L.E.D. patients produced in rabbits neutralized the factor, while antibodies against normal human serum did not, it was concluded that the factor is a distinct component of the L.E.D. gamma globulin.[128] It is interesting that intensive treatment with ACTH or cortisone caused inactivation of the L.E. factor, while smaller but clinically effective doses had no such effect.[126] The presence of the L.E. factor in the serum and the fact that most cases occur in women in the reproductive age suggest that L.E.D. may be a metabolic disorder.

Pathological Chemistry.—The blood chemistry in L.E.D. differs from that in rheumatic fever and rheumatoid arthritis in that the total protein concentration is usually within normal limits.[255] It resembles that of these two diseases in that the serum albumin is low, while the globulins are elevated.[43,106,150] The rise in globulins is chiefly one in gamma globulin,[43,47,167,320] but during the acute phase the alpha globulins are also elevated.[126,127,167,255,290,291,320] The rise in globulins is associated with an elevation of the serum hexosamines from a normal level of 100 to 120 mg. per cent to 180 to 220 mg. per cent.[290] Boas and Reiner[32] found statistically significant correlation of hexosamines and gamma globulin, but of no other protein fraction. The total globulins and the hexosamines returned to normal following the administration of ACTH or cortisone, while the alpha globulins remained essentially the same.[126,127,255,290,291] The albumin of the sera of L.E.D. patients contained 0.29 per cent, and the gamma globulin 1.60 per cent, of hexosamine as compared with 0.34 and 1.58 per cent in normal sera, while the combined alpha 1 to beta fractions contained 5.15 per cent.[32] It was concluded from these observations that the changes in the mucopolysaccharides in L.E.D. patients reflect changes in gamma rather than in the other globulins.[32] This is difficult to accept because the total amount of the alpha and beta globulins is not much smaller than that of the gamma globulin, but the latter contains only one-third as much hexosamine as the former. The nonspecific hyaluronidase inhibitor may also be changed in L.E.D. The collagenase inhibitor was found to be significantly depressed in subacute L.E.D.[300] This is probably related to the drop in the albumin fraction in which it is contained.

The significance of the drop in albumin and the rise in alpha globulins and hexosamines in L.E.D. is probably the same as in rheumatic fever and rheumatoid arthritis. The drop in collagenase inhibitor may signify a disturbance of the normally balanced mechanism of collagenase and its inhibitor resulting in alteration of the mucopolysaccharides of the patient, as suggested by Stoughton and Lorincz.[300] The rise in gamma globulins, on the other hand, is not fully explained. The presence of the L.E. factor in this fraction suggests that it is significant etiologically.

Chemical analysis of the *joint fluid* in L.E.D. revealed a high concentration of hyaluronic acid with low viscosity.[265,266] This suggests depolymerization of the mucopolysaccharides.

Pathological Morphology.—The morphological changes in L.E.D. have been ably described by Klemperer and associates.[155,158,159] The structures most often involved are the skin, serosal membrane, heart, blood vessels, and kidneys. However, other elements, such as the joints and skeletal muscles, are also frequently affected.

The characteristic lesions of L.E.D. consist of an increase in the amount and density of the ground substance (mucoid degeneration) and a straightening and thickening of the collagen fibers (or the deposition of a similar material) showing intense eosinophilia and refractibility in hematoxylin-eosin-stained sections and staining red with Mallory's trichrome stain and deep mahogany with silver (fibrinoid degeneration). The basement membranes show a striking increase in thickness and staining intensity, due either to disintegration with liberation of 1,2 hydroxyl groups,[301] or to imbibition with plasma components. The fibroblasts and macrophages in the affected areas show pyknosis, karyorrhexis, and other evidence of disintegration. This is associated with, or followed by, a more or less heavy infiltration with polymorphonuclear leucocytes, plasma cells, and lymphocytes and the proliferation of fibroblasts. Miliary granulomas including epithelioid cells were found in the serosal membranes by Teilum.[310]

The changes in the skin in L.E.D. are specific enough to differentiate this disease from other maladies clinically. The endocardial lesions known as Libman-Sacks endocarditis occur in no other disease. The myocardial lesions are not specific; Aschoff nodules are not observed.[159] The vascular alterations range from fibrinoid degeneration to complete fibrinoid necrosis. The vessels especially affected are the smaller arteries and arterioles.

The renal lesions in L.E.D. differ from those in other collagen diseases by heavy thickening of the basement membrane (wire looping). In early cases the membrane stains deeply red with hematoxylin-eosin or pink or red with Mallory's trichrome stain (fibrinoid degeneration), but later it may stain blue with the latter stain and thus react like collagen (collagenization). In more severe cases the loops may become completely necrotic (fibrinoid necrosis). Two of twenty cases also showed evidence of "true" glomerular nephritis. Wire looping was not observed in

rheumatic fever or periarteritis nodosa, but it was present in five of forty-two cases of glomerular nephritis unrelated to L.E.D. In the latter cases, however, typical changes of glomerular nephritis were present as well.[158]

It is noteworthy that Teilum[311] observed the presence of paramyloidosis in L.E.D., and that Aegerter and Long[2] found it in four of their five cases. This observation deserves further study.

Generalized Scleroderma

Generalized scleroderma may appear acutely and progress rapidly, but more often the onset is gradual followed by a chronic course. Most cases occur in patients in the fourth and fifth decades. Women are affected twice as often as men. The prognosis is relatively favorable. Death, if it occurs, may come early, in acute cases, but it usually occurs late in the disease.

The cause of generalized scleroderma is unknown. There is no evidence of infection or the anaphylactic type of allergy.[16,155,194] Patients with generalized scleroderma have been found to be hypersensitive to sunlight.[22,308] It has been suggested that this may be due to "pathergy" (unspecific hypersensitivity) caused by substances other than antibodies.[194] These substances may be catalysts. Protein balance studies in patients with generalized scleroderma[314] revealed a state of prolonged protein attrition differing from protein depletion in starvation or Cushing's syndrome. This has been interpreted to mean that the patient cannot maintain chemical integrity, but substitutes collagen for the usual components, resulting in the deposition of pathological proteins. This view is in keeping with the observation that a high protein diet reduces the induration of the involved skin.[314] The greater incidence of generalized scleroderma in women and the observation of remissions at the onset of menstruation followed by exacerbations afterward and of low ketosteroids in the urine[195] suggest endocrine involvement.

Pathological Chemistry.—The chemical alterations in generalized scleroderma have not been studied well. Hyperproteinemia was noted in a patient investigated by Talbott and associates.[308] Hyperglobulinemia has been found in several acute cases.[22,329] Albumin was moderately depressed and gamma globulin markedly elevated, with no significant change of the other globulins, in thirty patients studied in three laboratories.[167,170,320] Calcium and phosphorus levels were found to be normal.[164] Urinary studies frequently show increased creatine excretion.[22] The latter is explained by the muscular involvement in this disease.

Pathological Morphology.—The visceral manifestations of generalized scleroderma have been reviewed extensively by Beerman.[25] The structures most commonly involved are the skin and adjacent tissues. Other structures frequently affected are the skeletal muscles, heart and vessels, tendons, fasciae and periosteum, the serosal membranes, the intestinal tract from mouth to colon, the kidneys, and the lungs. Arthritis was found in some early cases by Baehr and Pollack[16] and in one-half of the cases by Banks.[22]

The morphological alterations in generalized scleroderma have been restudied recently by several investigators.[16,155,159,194,239] It has been found that the disease begins with edema and an associated increase in ground substance (mucoid degeneration) with or without fibrinoid degeneration, although the predominating change from the beginning is usually a diffuse increase in fiber formation leading to increase in bulk and density of the connective tissue (sclerosis).[16,155,159]

Marked involvement of small arteries and arterioles was noted in patients who died during the acute phase of the disease.[22,31,194,239,308] In moderately severe cases "mucinous material which had the appearance of Wharton's jelly" was found in the intima within the limits of the lamina elastica interna.[308] In more severe cases fibrinoid degeneration and necrosis occurred in this location.[22,31,194,239] The latter was associated with, or followed by, heavy infiltration with leucocytes and later by cellular proliferation in all layers of the vessels, leading to organization of the fibrinoid material and often to obliteration of the lumen. The ultimate outcome was sclerosis. It appears that the vascular alterations are not the cause of the general sclerosis in this disease, but the two occur simultaneously and independently. This view is supported by the finding of

no or insignificant vascular changes in milder cases of this disease and by differences in distribution of the vascular and connective tissue changes as demonstrated in the heart.[229]

Aschoff bodies were not observed.[159,229] No alteration of the basement membranes was found in the skin,[301] but changes of the glomeruli resembling the wire looping and fibrinoid necrosis of lupus erythematosus disseminatus were described by several investigators.[22,31,239]

It has long been known that generalized scleroderma is often associated with calcification of the skin.[143,161] This may be so extensive as to obscure the diagnosis of scleroderma. The calcification occurs, according to Beerman,[25] almost exclusively in women. As the serum calcium and phosphorus levels as well as serum phosphatase concentrations are normal, this calcification cannot be looked upon as a result of hyperparathyroidism. The presence of a negative calcium balance suggests retention of calcium in the altered connective tissue.

Dermatomyositis

This disease may occur in an acute, subacute, or chronic form, but it usually is chronic. The onset may be acute, but more often it is gradual. Relapses and exacerbations are frequent. The disease occurs mostly in children and young persons up to 40 years. It affects both sexes with equal frequency. The mortality is about 50 per cent.[22]

The cause of dermatomyositis is obscure. O'Leary and Waisman,[227] who observed forty "unquestionable" cases, pointed out that the onset of the disease is frequently preceded by acute infections, such as sore throat, sinusitis, or other upper respiratory infections, suggesting an infectious etiology. However, there seems to be no immunological evidence for this contention. It was noted that patients with dermatomyositis may be markedly sensitive to sunlight.[22,318]

Pathological Chemistry.—Total proteins were usually low, and the albumin-globulin ratio was normal, in the cases studied in this respect by O'Leary and Waisman,[227] but nine of their patients had an increased sedimentation rate, indicating an elevation of fibrinogen or globulins or both. Frank hyperglobulinemia was recorded in one of Kinney and Maher's cases.[154] Recent studies of seven patients in three laboratories revealed a significant drop in albumin and a moderate to marked elevation of gamma globulin.[47,167,320] The inhibitor of collagenase was likewise depressed in the one patient studied.[300] Urinalysis of patients with dermatomyositis usually shows increased excretion of creatine. This is explained by the muscular involvement in this disease.

Pathological Morphology.—The morphological alterations in dermatomyositis have not been described as well as those in other collagen diseases. The various case reports which have appeared in recent years[22,154,227,231,318] seem to show that the disease affects particularly the skeletal muscles and the skin. In eighteen of the forty cases reported by O'Leary and Waisman[227] the muscles were affected before the skin became involved; in two cases the skin remained entirely free of the disease. Heart, blood vessels, serosal membranes, mucous membranes, and other structures may also be affected. Objective evidence of heart disease was obtained in nine of the forty cases studied by O'Leary and Waisman.[227] The involvement of the blood vessels has been stressed since Fahr pointed this out.[76] Joint pain is also a common feature;[22] however, it is not certain whether this is due to alteration of the joints or to muscular changes. Renal involvement, on the other hand, has apparently not been described.

The lesion of dermatomyositis appears to be characterized by mucoid degeneration with or without fibrinoid degeneration, infiltration with lymphocytes and plasma cells, and fibrosis of the connective tissue, and by degeneration and necrosis of muscle fibers. The basement membranes of the skin show changes resembling those in L.E.D.[301] It appears that the connective tissue reacts at first with an increase in ground substance.[231,318] This is associated with, or followed by, infiltration with lymphocytes and plasma cells. Fibrinoid degeneration followed by conversion of the deposited material into a filmy mesh staining like collagen (collagenization) has also been described.[231] The ultimate outcome is sclerosis.

No remarkable vascular changes were observed by O'Leary and Waisman.[227] However, Banks[22] found "edema" and infiltration with lymphocytes and plasma cells of blood vessels in

some cases. Pagel and associates[231] described the deposition under the endothelium of arterioles of fibrinoid material in early severe cases. Hyalinization of the arteriolar wall associated with narrowing of the lumen was noted in older cases.[184,318]

The muscular changes in dermatomyositis consist of degeneration and necrosis of muscle fibers followed by scar formation. They differ from those in generalized scleroderma in that they are more severe. The heart muscle may be affected as much as the skeletal muscles. Aschoff bodies, however, have not been reported.

It is noteworthy that the skin, if affected may undergo calcification. Of the forty cases reported by O'Leary and Waisman,[227] five developed calcinosis of the skin. The cause of this complication is obviously the same as in generalized scleroderma.

Serum Sickness

Serum sickness is an acute disease of varying intensity. It usually terminates in recovery. Death, if it occurs, is due as a rule to the disease for which the serum was given.

It is well established that serum sickness is an allergic reaction due to intravenous injection of foreign serum or other foreign proteins. If 100 ml. of serum or more are given, 90 per cent of the patients develop evidence of the disease; if less than 10 ml. are administered, only about 10 per cent develop symptoms.[182] It is generally believed that the disease is caused by reaction of the injected antigen with antibody fixed in or on smooth muscle cells, vascular endothelium, and other mesenchymal elements (Arthus reaction). The belief that this is mediated through release of intracellular histamine[258] is not supported by evidence.[52,82,261] The first signs of the disease, following one injection of serum, develop as a rule after a latency period of six to twelve days, which is the time required for production of significant antibody titers.

Serum sickness has frequently been reproduced experimentally. It has been demonstrated that the disease commences only after precipitins appear in the circulating blood, that severe serum sickness develops only in the presence of high antibody titers,[183] and that recovery from the disease is conditioned by disappearance of antigen.[176] A transient depression of serum complement was demonstrated by several investigators in animals.[271,324] As in man, large doses of foreign protein are more effective than small doses. Younger rabbits are more susceptible than older animals,[72] and albino rabbits react more severely than chinchilla rabbits;[281] this indicates constitutional differences in various hosts.[258] It has also been demonstrated that serum sickness caused by a single injection of foreign protein usually has a subacute course, while a second injection during the third week often causes a more acute disease.[72]

That serum sickness may be suppressed by stimulation of the adrenals was first shown by Forman and associates (1948, 1949).[83,84] Similar results were obtained with ACTH and cortisone.[30,92,93,281,294] Adrenalectomy, on the other hand, caused aggravation of serum sickness.[50] The suppressing effect of ACTH and cortisone was first explained by the demonstrated depressing action of the 11-oxy- and hydroxycorticosteroids upon antibody formation by lymphoid cells.[83,84,92,93] This appears to be a major factor in the case of larger doses of ACTH and cortisone.[93] The recently observed amelioration of the disease by smaller doses of ACTH, which do not suppress antibody formation,[294] is not explained. It may be that the 11-oxy- and hydroxycorticosteroids act through their delayed depressing effect upon capillary permeability[26] by suppressing exchange of antigen and antibody between blood and tissues, or they may alter the capacity of smooth muscles and connective tissue to fix antibody or to react to the interaction of antigen and antibody.[324] The immediate depressing action of these hormones upon the permeability of synovial tissue[279] cannot be called upon to explain this situation, because other steroids, though depressing the permeability of this tissue, do not suppress serum sickness.[281]

Pathological Chemistry.—Moore and Waugh[218] demonstrated increased coagulability of the blood during the first week following the injection of serum. Forman and associates[72] have shown that this is associated with a rise in platelets and histamine which, in rabbit's blood, is largely contained in the platelets. These changes are followed by a rise in mast cells which are believed to produce heparin. As these various alterations occur before significant quantities of antibodies are formed and as the rise in platelets resembles that following infections, exposure to ultraviolet light, and other injuries,[110] they are regarded as nonspecific and nonallergic reactions to injury.[82]

The blood proteins in serum sickness are apparently not significantly altered. The sedimentation rate is usually within normal limits.[182] However, the demonstrated rise in antibodies leaves no doubt that the gamma globulins are changed.

Pathological Morphology.—The pathological alterations caused by serum in man have been well described and illustrated.[42,67] The organs most severely affected are the heart, the blood vessels, and the kidneys. Lungs, liver, and skin may also be involved. Arthritis occurs in 50 to 60 per cent of patients receiving large amounts of serum.

Two patients who received 265 ml. of antimeningococcus serum within ten days and 600 ml. of antipneumococcus serum within eight days, respectively, and who died twelve and ten days, respectively, after the first injection showed chiefly edema and proliferation of mesenchymal cells (fibroblasts, endothelial cells, plasma cells, lymphocytes) in endocardium, myocardium, and pericardium, in the intima and adventitia of arteries and veins, and in the connective tissue of lungs, liver, kidneys, and other organs.[42] One patient, who died thirty days after the first injection of a total of 2,000 ml. of serum, also revealed necrotizing arteritis of the coronary arteries. There were fibrinoid degeneration and necrosis in the media associated with infiltration of leucocytes and proliferation of mesenchymal cells. No alterations were observed in twenty-one patients who died during the first seven days following injections of serum.[42]

The morphological alterations in experimental animals have been well described by several investigators;[11,72,160,192,255,259] they closely resemble those in man. Proliferation of fibroblasts, endothelial cells, and plasma cells occurs especially in endocardium, myocardium, and pericardium, in intima and adventitia of arteries and veins, in the septa of the lungs, and in the kidneys.[11,72] Animals sacrificed eleven days or more after the first injection of serum frequently show valvular lesions which differ from those in rheumatic fever in that they are essentially proliferative, and they are located at the base of the valves rather than at the closing edge. They also show focal degeneration and disintegration of heart muscle fibers surrounded by proliferating mesenchymal cells.[11,72,174] Occasional accumulations of mesenchymal cells resembling Aschoff bodies,[141,149,258,259] but not identical therewith,[15,72,221] are likewise observed. The arteries of the rabbits sacrificed eleven days or more after the first injection of serum frequently reveal a peculiar segmental "edema" with swelling of muscle cells and loss of definition of their nuclei followed by proliferation of mesenchymal cells, especially in the intima and adventitia.[72,201] The kidneys at this time often show swelling and proliferation within the glomerular tuft, which has recently been identified as an intercapillary glomerular reaction differing from diffuse glomerular nephritis by the absence of endothelial proliferation.[70]

Rabbits sacrificed shortly after a second injection of serum often exhibit fibrinoid degeneration and necrosis of the arteries followed by infiltration with leucocytes and proliferation of mesenchymal cells[72,160,216,258,259] and acute focal glomerular nephritis characterized by partial necrosis of loops, exudation of a fibrinoid material into the capsular space, and subsequent organization by epithelium (crescent formation).[72] Fibrinoid degeneration in endocardium and myocardium is likewise observed.[258] These more serious alterations were seen mostly following a second injection of serum. They occurred after the first injection only in some susceptible albino rabbits receiving large doses of serum.

It thus appears that the injection of foreign protein is followed by successions of lesions beginning with cellular proliferation and followed by typical Arthus reactions. The proliferation of plasma cells early during the disease has apparently to do with the production of antibody rather than the result of antigen-antibody union as pointed out elsewhere.[68] The Arthus reactions in arteries and kieneys are of two distinct types. There is a subacute type, characterized morphologically by swelling and proliferation, presumably due to a gradual reaction between the diminish-

ing antigen and the slowly rising fixed antibody, and an acute type characterized morphologically by fibrinoid degeneration and necrosis and due to a sudden clash of freshly injected antigen with a considerable amount of fixed antibody.[72] These reactions are distinct in many cases, but blend into one another in others.

Periarteritis Nodosa

This disease is a subacute or chronic malady often with an acute onset. It may occur at any age; one-half the number of patients reported in the literature were in the third or fourth decade. Men are three to four times as frequently affected as women.[13,22,105] The duration of the disease is from three months to five years.[40] The average duration has been estimated at five months.[164]

The arterial changes in periarteritis nodosa resemble those in serum sickness so closely that the two appear to be the same. For this and other reasons, it is believed that periarteritis nodosa is an allergic disease due to an Arthus reaction. The antigen is difficult to demonstrate. Antistreptolysin O is apparently normal.[253] Recent observations seem to show that some cases of periarteritis nodosa may be caused by sulfonamides, thiourea, and similar chemical compounds.[9,257,258]

Periarteritis nodosa is frequently associated with severe asthma and marked eosinophilia.[45,151,246] This association was found in 18 per cent of 300 patients.[232] These cases, and those caused by drugs, have recently been separated as "hypersensitivity angiitis"[242] or "allergic angiitis and granulomatosis"[40] as first suggested by Otani.[230] It was pointed out that they differ from cases of "true" periarteritis nodosa not only by the presence of severe asthma and marked eosinophilia, but also by eruptions of specific granulomas in the general connective tissue. It was argued that, although the altered collagen appears as in other types of periarteritis nodosa, there must be a difference in its chemical composition, because it excites epithelioid and, particularly, giant-cell reaction.[40] Whether or not this separation is indicated remains to be seen. The absence of this lesion in fifteen patients with periarteritis without allergic history[40] can hardly be accepted as evidence, for different organ responses to different antigens have been observed also in serum sickness.[134] As four of the fifteen patients with true periarteritis nodosa reported by Zeek and associates[242] suddenly developed urticaria and eosinophilia during the last few weeks of life with no previous recognized manifestations of allergy, it may be best at present to consider the two types as variations of the same disease rather than distinct entities.

Certain animal experiments have led to the suggestion that periarteritis nodosa may be partly due to hypertension.[284] It should not be overlooked, however, that the lesions caused by these procedures were called by Klemperer[87] not "periarteritis nodosa," but "hyalinized and necrotic vascular lesions." In human periarteritis nodosa hypertension is often observed. It was noted by Griffith and Vural[105] in thirteen of sixteen cases of periarteritis nodosa and by Churg and Strauss[40] in seven of thirteen cases of "allergic angiitis." However, all hypertensive patients with the disease showed periarteritis in their kidneys, and all but one with such renal changes had hypertension.[105] Moreover, hypertension occurred particularly in cases of longer duration and, as a rule, in the latter part of the disease.[40,105] These observations suggest that hypertension in human periarteritis nodosa is secondary to renal involvement, rather than a factor in its etiology.

Pathological Chemistry.—Hyperproteinemia and hyperglobulinemia were noted by several investigators.[150,292] Plasma protein fractionation by Cohn's procedure revealed an increase in the N content of fractions II and III containing alpha 2, beta, and gamma globulins and a decrease in fraction V containing albumin; there were no characteristic changes in lipid values.[233] Cooling at 4° C. for twenty-four hours caused spontaneous precipitation in the serum of a protein which electrophoretically behaved like gamma globulin. It differed from previously reported "cold fractions" or "cryoglobulins" in not redissolving at room temperature.[168] The demonstrated rise in gamma globulin is in keeping with the view that periarteritis nodosa is an allergic disease.

The serum mucopolysaccharides and the nonspecific hyaluronidase inhibitor were found to be elevated in one patient studied by Kelley and associates.[153]

Pathological Morphology.—Most descriptions of the morphological alterations in this disease pertain to the arteries. Involvement of the general connective tissue is suggested by casual observations of fibrinoid degeneration and necrosis, inflammatory infiltrations especially with eosinophils, and granulomas consisting of epithelioid cells and giant cells.[196,257,258,263,285] These observations were amplified recently by the demonstration of lesions in the general connective tissue consisting, first, of inflammatory cells, especially eosinophils, and, later, of epithelioid cells and giant cells of Langhans' type associated with varying numbers of plasma cells and lymphocytes.[40,342] The core of the granulomas contained necrotic cells, especially eosinophils, and showed marked fibrinoid degeneration and necrosis. These changes were most frequent in the connective tissue of the heart, especially in the epicardium, but they occurred also in lungs, spleen, kidneys, lymph nodes, skeletal muscles, and skin. The cutaneous lesions were recognized clinically as deep cutaneous or subcutaneous nodules in one-half the number of patients. Their ultimate fate was replacement by scar tissue (sclerosis). On the other hand, Aschoff bodies have not been observed.[40,155,196]

The arteries involved in periarteritis are usually of medium and smaller size. Weir[228] found none larger than 1.5 mm. in diameter. The structures most frequently affected are kidneys, mesentery, spleen, lungs, liver, heart, and the gastrointestinal tract, but other organs such as the skeletal muscles may also be involved.

The arterial lesion is definitely segmental. It closely resembles the acute arteritis of serum sickness. It commences with fibrinoid degeneration and necrosis of the inner portions of the media. This is followed by marked infiltration with polymorphonuclear leucocytes, eosinophils, and other elements in intima, media, and adventitia and by proliferation of mesenchymal cells in intima and adventitia. The ultimate outcome is fibrosis and scar formation (sclerosis).[13,22,80,114,194,196] "Edema" associated with, or preceding, the fibrinoid degeneration and necrosis was also noted.[13]

It was pointed out earlier that the allergic arteritis in serum sickness occurs in an acute and subacute form. If periarteritis nodosa is essentially the same as serum sickness, we should expect to see subacute periarteritis nodosa as well. That this may exist is suggested by the observation of accelerated and retarded forms.[196] It is conceivable, however, that the subacute form, if it occurs, has a course so mild that it is not recognized clinically and hence escapes detection.

PHYSIOLOGICAL-PATHOLOGICAL CORRELATIONS

If we look upon the *morphological manifestations* of the various collagen diseases, we find that some are common to all, while others differ significantly. The *common changes* may be defined with Klemperer, Pollack, and Baehr[159] as *systemic* alterations of the mesenchyme connecting organized structures (connective tissue). The nature of these alterations varies with the clinical course of the maladies. All appear to begin with increased production of ground substance (mucoid degeneration) indicating disturbed activity of fibroblasts. In severe or acute cases, such as acute L.E.D., acute generalized scleroderma, acute dermatomyositis, acute rheumatic fever, acute serum disease, and acute periarteritis nodosa, this may be associated with, or followed by, fibrinoid degeneration and necrosis believed to be due to precipitation of acid mucopolysaccharides with fibrinogen and probably other proteins, possibly, in part, of local origin.[7,5] In less severe or subacute cases, notably in later stages of rheumatic fever, in subacute serum sickness, in subacute periarteritis nodosa, and in certain stages of rheumatoid arthritis, the initial alterations are followed by considerable proliferation of fibroblasts and their undifferentiated predecessors, of plasma

cells, and of other mesenchymal elements. Late stages or chronic cases are characterized by sclerosis with or without hyalinosis. These various changes may be associated with, or followed by, amyloidosis (rheumatoid arthritis) or paramyloidosis (L.E.D.), believed to be due to precipitation of mucopolysaccharides with globulins or related proteins. There may be considerable overlapping or transformation of one lesion into another, particularly in cases changing from an acute to a subacute or chronic phase. The various collagen diseases thus have in common two factors: not only are they characterized by systemic alterations of the connective tissue, but also they develop the whole scale of morphological changes which are known to occur in this tissue.

The *morphological differences* of the various collagen diseases are characteristic enough to be more or less diagnostic. The heart is most prominently involved in rheumatic fever; the vessels in periarteritis nodosa, serum sickness, L.E.D., and generalized scleroderma; the joints in rheumatoid arthritis and rheumatic fever; and the skin in dermatomyositis and generalized scleroderma. The cardiac changes in rheumatic fever are distinct from Libman-Sacks endocarditis in L.E.D. The medium-sized arteries are involved in serum sickness and periarteritis nodosa, the smaller arteries and arterioles in L.E.D., their intima in generalized scleroderma, and the arterioles in dermatomyositis. The joint lesions in rheumatic fever are distinct from those in rheumatoid arthritis. The subcutaneous nodules in rheumatic fever differ from those in rheumatoid arthritis, and both differ from those in periarteritis nodosa. Striking differences in renal lesions also exist. L.E.D. is characterized by wire looping, i.e., infiltration of the basement membrane of the glomeruli with mucoprotein. In serum sickness, and probably also in periarteritis nodosa and rheumatic fever, we find a reaction of the glomerular mesenchyme contained in the intercapillary space (intercapillary glomerular nephritis); this may or may not be associated with fibrinoid exudation into the capsular space (extracapillary glomerular nephritis). There are also distinct differences in the proliferative reactions in the various collagen diseases. Rheumatic fever is characterized by Aschoff bodies, rheumatoid arthritis by granulations containing follicular accumulations of lymphocytes, and subacute serum sickness and periarteritis nodosa by segmental allergic proliferations in the arteries. These various differences do not detract from the characterization of the collagen diseases as systemic alterations of the connective tissue involving the whole scale of mesenchymal reactions. They merely show that these diseases are otherwise quite heterogeneous.

If we consider the *chemical and serological alterations* of the various collagen diseases, we find again that some are common to all, while others differ significantly. Serum albumin was found to be depressed in the five collagen diseases in which this was studied. The collagenase inhibitor which migrates with the albumin fraction was likewise depressed. On the other hand, fibrinogen, the alpha globulins, the C-reactive protein, the mucopolysaccharides, and the nonspecific hyaluronidase inhibitor (which may be heparin) were elevated during the acute and subacute stages, followed by their return to normal during remissions or in convalescent patients in the various collagen diseases in which they were studied. The only exception was scleroderma in which the alpha globulins were

found to be normal, but this is a very chronic disease. The depression of albumin suggests liver injury. The elevation of the alpha globulins and other proteins and of the mucopolysaccharides appears to be well correlated with evidence of mesenchymal injury, such as depolymerization of the hyaluronic acid in the joint fluid, and mucoid degeneration and fibrinoid degeneration and necrosis of the connective tissue generally. It also occurs in many other acute and subacute maladies affecting the connective tissue. Hence, it is reasonable to regard them as unspecific sequels of the morphologically visible alterations of the connective tissue, reflecting the severity and extent of injury rather than its cause. The observation that some of these components return to normal more slowly than others following administration of ACTH or cortisone suggests different mechanisms. It appears that some of these changes may be due to leakage of normal or pathological tissue components through connective tissue membranes whose permeability is altered by depolymerization or destruction of their mucoproteins. Others may be the result of alterations of fibroblasts or other cells involved in the elaboration of these materials.

The gamma globulins have been found to be elevated in all collagen diseases except serum sickness. In the latter disease the blood proteins were usually found to be normal. The demonstrated rise in antibody, however, implicates the gamma globulins in this disease also. The rise in gamma globulins in rheumatic fever is correlated in part with the rise in the various specific antibodies involved in this disease. In L.E.D. it is associated with a rise in the specific L.E. factor contained in the gamma globulin fraction. The rise in gamma globulin in generalized scleroderma and dermatomyositis is not yet explained. However, its source appears to be clear. Collagen diseases are characterized by an increase in plasma cells in the diseased connective tissue, in the bone marrow, and elsewhere. There is strong evidence that these cells are the cellular sources of antibodies and other gamma globulins.[69]

The *serological and chemical differences* of the various collagen diseases are again characteristic enough to be of diagnostic significance. Rheumatic fever is characterized by high titers of antistreptococcal antibodies, rheumatoid arthritis by strong unspecific agglutination reactions, L.E.D. by the specific L.E. factor, and serum sickness, and probably also periarteritis nodosa, by specific precipitins. It is possible that all these factors are antibodies, but it is more likely that some are abnormal gamma globulins unrelated to antigen. How ever this may be, the different character of these factors shows clearly that these maladies are not the same.

SUMMARY

Summarizing these various correlations, we may say that the collagen diseases are characterized by injury of the connective tissue which consists of mucopolysaccharides and proteins produced by, or with the aid of, fibroblasts from materials derived from blood and other sources. This injury, if severe enough, is associated with, or followed by, a rise in the blood of mucopolysaccharides, the nonspecific hyaluronidase inhibitor (probably heparin), alpha globulins, fibrinogen, and other components derived apparently from the injured mesenchyme, and

a drop of albumin and the collagenase inhibitor, apparently implicating the liver and possibly other organs. The injury of the connective tissue is associated with, or preceded by, an elevation of gamma globulin, or components of this fraction, containing agents such as antibodies or the L.E. factor which are involved in the causation of the injury. Antibodies and other components of the gamma globulin fraction are apparently formed by plasma cells. Proliferation of these cells is a common occurrence in collagen diseases. It may be postulated, therefore, that *the common denominator of the various collagen diseases lies in their pathogenesis or, more precisely, in the production by these dieases of abnormal gamma globulins apparently by plasma cells causing injury of the general mesenchyme.*

If this concept is correct, we will understand why myxedema is not classified with the collagen diseases. It is true that this disease is characterized by systemic alteration of the connective tissue, but this is not due to abnormal gamma globulin, but to a change of the thyroid or pituitary gland. Malignant arteriolar sclerosis and Buerger's disease, classified with the allergic diseases by Klinge,[160] differ from collagen diseases in that they do not affect the connective tissue systemically. However, "primary amyloidosis" or paramyloidosis is a primary systemic disease of the connective tissue probably caused by abnormal proteins produced by plasma cells. Its classification with the collagen diseases would be in keeping with the observation of paramyloidosis or similar disorders in L.E.D. and rheumatoid arthritis.

It may be pathogenetically significant that alterations of the hypothalamic-anterior pituitary-adrenal cortical axis have been observed in several collagen diseases and that both the physiology of the connective tissue and the course of the various disease processes may be altered by the 11-oxy- and hydroxycorticosteroids. The alleviating action of ACTH and cortisone may be "pharmacological" in part. However, in sufficient doses cortisone destroys plasma cells and other lymphoid cells and thus suppresses antibody formation. It enhances protein catabolism and thus causes a more rapid degradation of antibodies and other noxious proteins. It suppresses the permeability of connective tissue membranes and thus interferes with the exchange of components between blood and tissues. It is closely associated with the ascorbic acid metabolism and thus with the formation and maintenance of connective tissue. It also interferes with the proliferation of fibroblasts and the production of collagen fibers. Observations like these suggest that cortisone is effective through action upon the pathogenesis of the collagen diseases.

CONCLUSIONS

Collagen diseases are etiologically heterogeneous, but pathogenetically well-defined, maladies characterized morphologically by systemic alterations of the connective tissue and chemically by changes in the composition of the blood, reflecting both cause and effect of the injury.

The morphological alterations include the whole scale of tissue changes which occur in connective tissue. The degenerative alterations and some proliferative changes are results of the injury, and sclerosis resembles scar formation. The collagen fibers may or may not be involved. Hence, it would be better to

speak of *systemic diseases of the connective tissue* or *desmoses* instead of collagen diseases, as recognized by Klemperer.[156]

Many of the chemical changes are likewise the results of injury. The rise in the blood of mucopolysaccharides, of the nonspecific hyaluronidase inhibitor, of alpha globulins, of fibrinogen, and of other components reflects the alterations of the connective tissue, while the drop in albumin and in the collagenase inhibitor implicates the liver.

The proliferation of plasma cells and the elevation of gamma globulin, or of components contained in this fraction which are produced by the plasma cells, on the other hand, appear to have pathogenetic significance. Although the cause of these changes varies with the etiology of the various collagen diseases, the effect is the same, namely systemic injury of the connective tissue. The collagen diseases may therefore be spoken of as *dysgamma-globulinemias*.

The old concept of Klemperer, Pollack, and Baehr[159] that these maladies were collagen diseases, however, has served its purpose, for it stimulated wide interest in these diseases, and it caused an extensive restudy of the physiology and pathology of the connective tissue.

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Book Reviews

HEART DISEASE IN PREGNANCY. By A. Morgan Jones, M.Sc., M.B. (Vict.), F.R.C.P. (Lond.) New York, 1951, Grune & Stratton, Inc.

This small book is excellent. In a brief concise manner it expresses what appears to the reviewer to be the best current opinion on all the important clinical aspects of heart disease in pregnancy.

Its brevity and conciseness make it easy to read. It should be in the library of every internist who is concerned with the subject.

J. J.

DAS ELEKTROKARDIOGRAMM. THEORIE UND KLINIK. By Hans Schaefer. Berlin-Göttingen-Heidelberg, 1951, Springer-Verlag, 556 pages with 345 figures and 11 tables.

The author states in his preface that this monograph is an attempt to apply the physical basis of our present knowledge of electrophysiological processes to all aspects of electrocardiography. The main emphasis is placed on electrocardiographic theory, but numerous examples of application to the various categories of cardiac pathology are given. Specifically, the electrocardiograms are interpreted in terms of such fundamental variables as conduction velocity, duration of excitation in single fibers, geometrical spread of excitation and repolarization, mass relationships of activated parts, and so forth. A title "Advances in Electrocardiographic Theory and Application to Clinical Interpretation" would convey more truly the concept and nature of this book which actually has no parallel in the recent electrocardiographic literature.

The book is based largely on the extensive experimental material of the author only partially published in German periodicals. It contains, in the words of the author, "a large number of new original papers, for which no further publication is contemplated." For this reason, the book is invaluable as reference for important material from one of the most prominent European laboratories.

For the American reader, the book is also very useful as a critical reference source for continental European electrocardiographic literature. The coverage of American literature, although considered to a greater extent than in other recent German monographs, is incomplete. The book would have gained by reference to Myers' large material on myocardial infarct, to Prinzmetal's work on auricular flutter and fibrillation, to the large American literature on subendocardial ischemia, spatial vectorcardiography, and intraventricular electrocardiography. However, to be fair, there is still more American literature quoted in Schaefer's book than there is continental European literature in some American electrocardiographic publications. Obviously, an electrocardiographic textbook with well-balanced international information is still to be written and is probably possible only by cooperation of an international team.

The treatment of the standard versus precordial leads is an interesting illustration of the development of electrocardiography in Germany during the past decade. Due to the interruption of communication during the war, Wilson and associates' fundamental paper on the precordial leads (1942) remained unknown at that time, and the theory of "unipolar electrocardiography," as a synthesis of local patterns, was never accepted in Germany as a basis for electrocardiographic interpretation. Therefore, electrocardiography developed in the direction of vector analysis from the standard leads. It must have been interesting for the German electrocardiographers to learn, after the war, of the work on the ventricular gradient by Wilson and by Ashman. Actually, the greater part of the book is devoted to theory and application of the ventricular gradient, on a

larger scale than in any other material known to the reviewer. The approach is based on Ashman's work, but exceeds it in scope and analytical detail. Analysis of the area vectors has proved so informative in various types of cardiac pathology that the author suggests the use of this method for routine clinical interpretation.

On the other hand, the development of the chest leads played only an auxiliary role in German electrocardiography, and precordial leads were considered important mainly in so far as they contributed to the vector analysis in the sagittal or horizontal plane. Consequently, the author develops a really comprehensive theory of vector analysis from precordial leads. Starting from this background, the possibility of recording of local patterns is investigated, taking as an arbitrary definition a quotient of potentials from local to more distant areas of 3:1. The possibility that local patterns can be recorded from V_1 or V_2 is remote. Curiously enough, very few illustrations of chest leads are given; out of a total of 349 figures not more than one dozen show the precordial leads V1 to V_6. The various types of pathology are discussed on the basis of the Einthoven leads and gradient analysis, while at the end of the book, in a chapter of only thirty-three pages, the clinical application of chest leads is summarized. The lack of proper integration of the information from standard and precordial leads is a defect in the organization of the book; actually some of the electrocardiographic interpretations in the main sections may be challenged on this ground. For instance, in Fig. 175a a wide QRS with an angle of the QRS area of 60 degrees is interpreted as uniformly delayed conduction in the absence of a typical right or left bundle branch block pattern in the standard leads. It is well known that the typical right or left bundle branch block pattern may appear only in the chest leads.

The book contains numerous interesting, and even startling, conclusions, but in the limited space of a book review only a few can be mentioned. From his calculations, Schaefer arrives at the conclusion that the extrinsic and intrinsic potentials cannot be differentiated in the precordial leads. This conclusion is verified by comparison of the electrocardiograms simultaneously recorded by means of a cathode ray oscillograph from the heart surface (a) by small bipolar electrodes with a few millimeters electrode distance which show the local potentials, (b) with unipolar recording from the two electrodes separately, using Wilson's terminal as indifferent electrode. The unipolar electrocardiograms (b) show a much wider QRS interval of approximately double amplitude. The true intrinsic deflection appears somewhere on the descending limb of the unipolar electrocardiogram. This shows that even from the heart surface unipolar electrodes record a mixture of intrinsic and extrinsic potentials which cannot be separated.

For explanation of some ST changes, it is assumed that there may be a decrement of conduction in damaged fibers, so that the excitation wave does not reach some more remote parts (asystole). The border between excited and asystolic parts will produce ST elevations in the direction of the asystolic region. ST elevations on such a basis could not be differentiated from true injury currents; it would depend mainly on the pathology which cause is more likely in a given case. The hypothesis of asystole may apply to delay of conduction in anoxia or ischemia, to disseminated infections, or to various toxic agents.

Hemodynamic factors are given greater importance than is usually the case. While this is offered as a working hypothesis, the interpretation of the T vector, of the U wave, and of some QRS changes, for instance in dilatation, is largely based on this concept. Undoubtedly, this question deserves further consideration.

On the basis of calculations, it is shown that uncomplicated ventricular hypertrophy cannot lengthen the QRS interval by more than 0.02 second, even when the weight of the heart increases up to three times. In fact, this may even be an overestimate, since the fibers in a hypertrophic heart are not only longer, but also thicker, and a thicker fiber conducts faster. This agrees with the fact that the conduction through the ventricular walls in normal hearts, at an estimated velocity of 1 M. per second, takes only a small fraction of the total QRS duration. Consequently, a greater QRS interval in ventricular hypertrophy indicates some disturbance of the conduction in the bundle branches and their ramifications.

For the understanding of the integrated vector the author's map of the direction of potentials on the heart surface in dogs is essential. The excitation seems to radiate from one center, near the sulcus interventricularis, but the spread is much too fast to be accounted for by muscular conduction. Interesting enough, extrasystoles produced in man and monkeys by stimulation from various areas seem to converge toward a center of roughly the same location. Vector analysis is systematically applied to ventricular ectopic beats, and on the basis of the frequency distribution of thirty-eight extrasystoles it appears that most extrasystoles originate near the bases, the next important region being the right ventricle. Very rarely, ventricular extrasystoles originate near the apex. It would be interesting to repeat these studies on a much larger material.

Of interest also are quantitative considerations of the relationship between magnitude of the ST elevation and size of the injury. It is estimated that, under optimum bipolar conditions, a single fiber may produce an injury potential of 7.5×10^{-5} mv. second area, so that around 700,000 fibers (only about 1/150 of the total heart mass) would be sufficient to generate a vector of 50 mv. seconds. In other words, comparatively small injured areas may produce sizable ST deviations. This is explained by the short duration of the action currents in the normal regions and their physiological cancellation due to their divergent directions.

The attempt is made to explain the various types of arrhythmias, including single extrasystoles, by a common mechanism, that of parasystole. Also, the role of sympathetic and vagal impulses is emphasized.

The consideration of hemodynamic factors leads to a different philosophy of electrocardiographic interpretation. The generally accepted procedure, at least in this country, is independent interpretation of the various clinical tests for the purpose of a synthetic diagnosis. In Schaefer's approach, all clinical information is indispensable for electrocardiographic interpretation which then becomes the last word or a meaningless appendix in the diagnosis, dependent on the circumstances. This means that in some cases errors made in the clinical diagnosis may affect the electrocardiographic interpretation. For example, in Figs. 63 and 64 two electrocardiograms from healthy persons are interpreted as normal, but the author says: "If the patient were clinically sick, nobody would hesitate to classify the ECG as abnormal." According to this reviewer's experience on large groups of normal population, both electrocardiograms are perfectly normal, not even borderline. It is doubted whether such an approach is workable for clinical electrocardiography.

One weak point of the book is the treatment of the statistical background for differentiation between normal and abnormal. Some electrocardiographic normal standards are uncritically accepted, and, in general, the differentiation between normality and abnormality is made on the basis of theoretical considerations rather than on the background of precise statistical information. However, the lack of adequate statistical analysis and appreciation of its importance has always been a somewhat sore point in electrocardiography, and Schaefer's book is, in this respect, no exception. As a rule, cases are presented as illustrations for an analysis of the changes in fundamental electrophysiological processes. The important question of how representative the cases are is left open. Such procedure depends to a large degree on the theoretical background of the electrocardiographer and lends itself easily, especially in the hands of less experienced electrocardiographers, to overinterpretation.

Since the book seems to be written mainly for those with some knowledge in electrocardiography, it actually does not matter too much whether one agrees or disagrees with the author's interpretation of some specific electrocardiograms. The merit of the book lies in the general considerations for application of theory in a given case, and these considerations are always interesting although the conclusions in regard to a given case may differ.

The analysis of some electrocardiographic abnormalities is summarized in tables which are useful for teaching purposes as well as for clinical interpretation. Taken all in all, the book is one of the most stimulating publications in the recent electrocardiographic literature and full of interesting suggestions for further work. It is regrettable that it is not as easily accessible to the average American electrocardiographer as American or British publications.

E.S.

FROM A DOCTOR'S HEART. By Eugene F. Snyder, M.D. New York, 1951, Philosophical Library of New York, 251 pages. Price $3.75.

Dr. Eugene F. Snyder has written an excellent book entitled *From a Doctor's Heart.* It contains a great deal of wisdom concerning many matters of common interest. Patients with heart disease, particularly those suffering from coronary artery disease, can obtain much comfort and valuable guidance in the conduct of their lives from these delightfully written pages. His discussion of the general care of coronary cases is sound and written in a very appealing style. Even physicians can learn much in the care of their patients from this book. The pattern of the author's discourse is artfully constructed; he uses his son and the questions he asks as the method of describing and explaining many medical problems. The book covers a good deal more than the field of cardiology from a lay and professional point of view. It discusses international relations, the glory of our democracy in contrast to the plight of totalitarianism, and many other topics of interest to all. Having lived in Russia and Czechoslovakia before coming to this country, Dr. Snyder was able to make sound comparisons between life here and abroad. In these matters, he displays a great deal of insight and emphasizes the spiritual values in modern life. This volume may be highly recommended to the medical profession and the lay public.

S.A.L.

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